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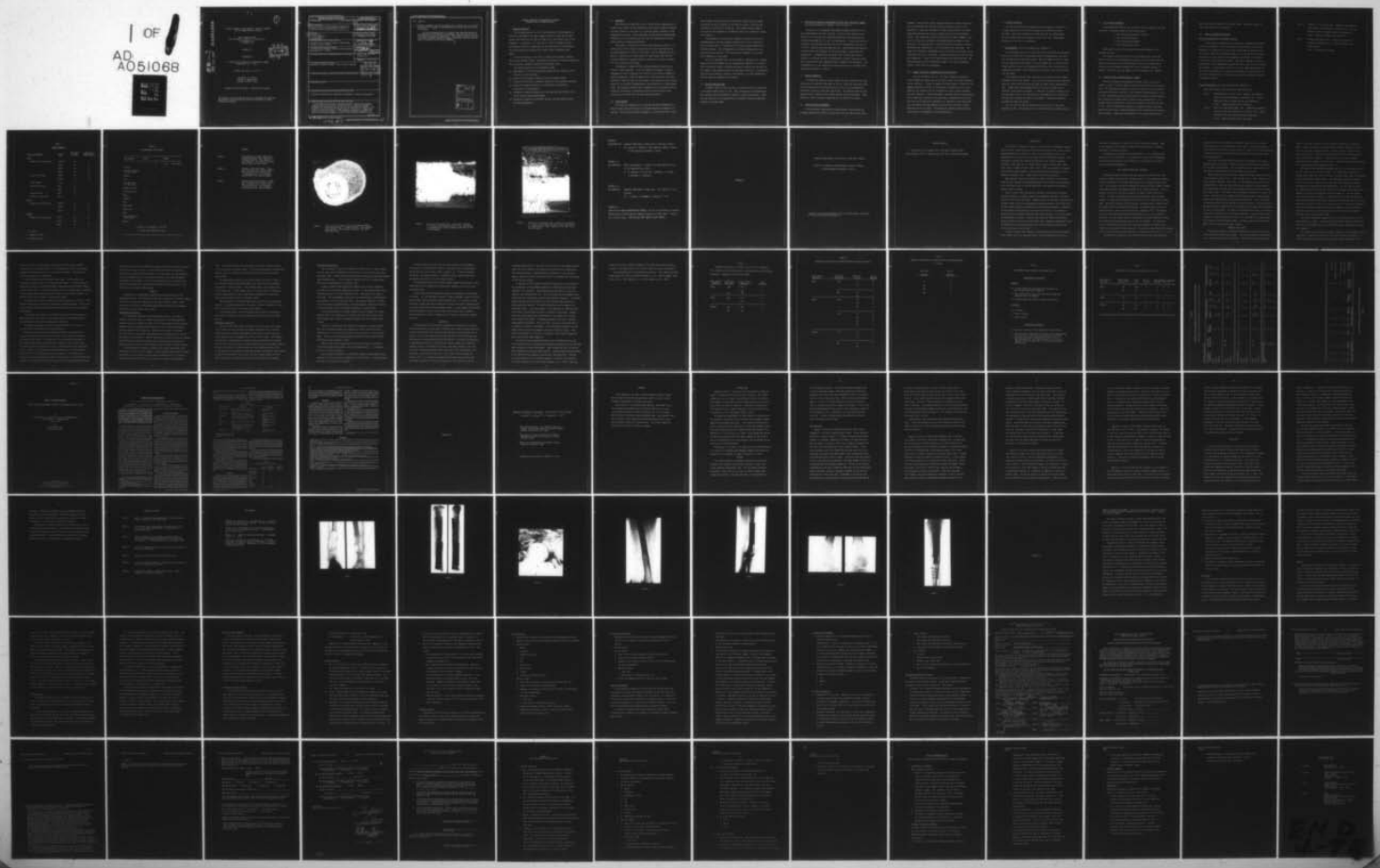

INTERNAL PROSTHETIC REPLACEMENT OF SKELETAL SEGMENTS LOST IN COMBAT RELATED INJURIES

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(FOR THE PERIOD 1 JULY 1976 - 30 JUNE 1977)

W. ROSTOKER, PH.D.
J. GALANTE, M.D.

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The objective has been to design prosthetic devices and clinical techniques which would allow reconstruction of a long bone damaged or diseased such that amputation may not be the necessary alternative. The research is pursued using the female baboon as the model. Large resections are used as the defect. The prosthesis assembly is designed to replace the resected segment; to allow a new union and regrowth of the

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residual fragments and the prosthesis into a single unit of calcified tissue which is capable of load bearing and function for the life of the patient.

It has been demonstrated in the model that these objectives can be attained by proper design of prosthesis, combined with the use of bone grafting and proper compression. With proper clinical procedure the proous prosthesis becomes invested by growing calcified bone and union is achieved with the bone fragments.

INTERNAL PROSTHETIC REPLACEMENT OF SKELETAL SEGMENTS LOST IN COMBAT INJURIES

I. TECHNICAL OBJECTIVE

The continuing objective of this investigation is the development of artificial replacements for large segments of bone or bones and the intervening joints which are lost due to trauma such as that which occurs in war casualties. In addition, it is felt that a civilian by-product of this investigation would be an application of the same system to the reconstruction following massive resections for certain types of malignant bone tumors.

The basic principle is the use of a special porous metallic material which allows ingrowth of bone. This permits the implant to become incorporated into the patients skeletal structure with functional union.

The specific objectives of the program include:

(a) Development of a series of biological models that are relevant to the eventual clinical situations.

(b) Study of the biological response of local and remote tissues.

(c) Evaluation of the bone in intimate contact with the prosthetic materials.

(d) Study of the long-term toxicity in animal models including the possibility of carcinogenesis.

(e) Evaluation of specific properties of the materials used from the viewpoint of their long-term performance.

(f) Design and evaluation of prosthetic devices including design studies for human implantation.

II. HYPOTHESIS

The prosthesis designs make use of a porous material manufactured by molding short lengths of fine titanium wire into precise shapes and bonding the wires (fibers) to each other by a sintering thermal treatment at high temperatures in vacuum. We have developed and perfected the manufacturing techniques in our own laboratories such that the technology may be transferred readily to industrial production.

The product is unique in its physical and mechanical properties. It posseses about 50% by volume of pores which are interconnecting and have inscribed diameters in excess of 100 microns. We have demonstrated over a period of eight years in a wide variety of animal models that bone and vascular elements will rapidly invade the pores and in a matter of months will invest the whole pore volume.

The material is highly elastic; having compliance characteristics similar to cancellous bone. It is also capable of permanent or plastic deformability which is necessary for clinical fit to end bone fragments by applied compression. While the product can be made from almost any metal available in fine wire form, we have chosen to work primarily with titanium because of its excellent biocompatibility and availability in high strength forms. The prosthesis designs involve composites of solid pieces which are strong and load bearing in conjunction with the porous material which carries little load but hosts the bony regrowth and union.

III. BASIC DESIGNS

The cortical configuration of a long bone has been synthesized by a tubular design whose profile and wall thickness matches the segment to be replaced. The cortical prosthesis component is a thin-walled tube of solid

high strength titanium sleeved with the porous titanium special product. The overlay of porous titanium for the baboon is about 1.5 mm thick and overhangs the solid tube at either end. The overhand permits complete fit up to the bone fragments by deformation under axial compression (using the AO device).

The prosthesis is provided with immediate fixation by the use of a intramedullary rod of high strength titanium which is also sleeved with porous titanium and by a titanium plate with screws applied diametral to the bone diaphysis. The intramedullary rod becomes incorporated in the long bone by bony invasion. The plate becomes submerged in callous but may be removed at a later date.

As will be described later, we have begun to experiment with a simpler design in which the segment and the intramedullary components are integral. This "rolling pin" design is sleeved with porous titanium over the whole of the segment; with overhand and over the medullary projections. The medullary projections are limited in length by the problems of clinical implantation but they should be sufficient for fixation.

IV. RELEVANT PUBLISHED WORK

A complete review of work by others on related subjects was presented in the annual summary report of 1974. Many investigators have demonstrated bone ingrowth into porous materials (metallic, ceramic and polymer). There has been relatively little application to prosthesis design and supporting research with animal models.

V. EVALUATION OF SEGMENTAL REPLACEMENTS OF BONE USING FIBER METAL IMPLANT

(See enclosed manuscript, Appendix I and see Table 1.)

The results of 43 segmental replacement prostheses inserted into 38 adult female baboons have been evaluated. Eleven of these implants are in animals still alive while the remaining animals have been sacrificed and evaluated radiographically as well as histologically. The results show that successful bone ingrowth occurred in 92% of the intramedullary rods and in 77% of the interface when bone graft was used. Uninterrupted bone formation was found across the prosthesis in 75% of the animals in which bone was transplanted. It appears from the results that, provided good initial stability is obtained and bone is transplanted, excellent long-term results can be obtained with bone ingrowth and bone bridging of the prosthesis. The biocompatibility of the composite was found excellent up to 60 months after implantation (Figures 1, 2 and 3).

VI. CONTROL PROSTHESIS

To increase the number of control animals in which prostheses were used which did not incorporate fiber metal at all or in part one additional baboon has been operated with a prosthetic device with two solid intramedullary projections instead of fiber metal projections. One further baboon has been implanted with a complete solid titanium implant without fiber metal. These animals are both in the early stages and not yet possible to evaluate.

VII. BONE TRANSPLANT EXPERIMENTS

In the previously operated and evaluated animals, bone grafting was performed chipping the cortical and cancellous bone into small pieces using

a hammer. This provides a bone transplant material of rather large pieces with a considerable bulk and with an uneven interface contact to the prosthesis. A study was initiated to evaluate the possibility of using a ground bone material which could be spread directly over the prosthetic surface. This experiment consists of replacing the femoral segment of one leg of a baboon with a prosthesis and transplanting bone grafts as done previously. On the other side a resection was made, a prosthesis inserted and ground bone transplanted. Six such procedures have been done. The animals are followed by radiography and two sacrificed at one month, two at three months and two at six months. Tetracycline labeling is used to study bone remodeling. To date five of these animals have been sacrificed. The remaining animals will be sacrificed in August. The early radiographic results of this study are encouraging.

VIII. CEMENT FIXATION OF INTRAMEDULLARY ROD PROJECTIONS

Clinical situations such as a very short metaphyseal proximal or distal fragment may require the use of acrylic cement to provide additional initial stability. In order to compare the effectiveness of fixation of the segmental prosthesis covered with fiber metal as compared to solid intramedullary rods cemented into the intramedullary canal, animal experiments have been conducted. In these experiments one baboon femur has been replaced with a fiber metal prosthesis with fiber metal intramedullary projections, the other with a fiber metal prosthesis with cemented-in solid projections. Four such animals have been operated, two have been sacrificed at three months and two at six months. The animals are currently under evaluation histologically, radiographically and biomechanically.

IX. ROLLING PIN DESIGN

In order to facilitate the implanting of the prosthesis, particularly in human application, the rolling pin design of a prosthesis has been developed. Three such prostheses have been implanted into baboon femurs and are currently one at nine months, and two at one year. Radiographic evaluation at this time is satisfactory.

X. CARCINOGENESIS (See enclosed manuscript, Appendix II)

The carcinogenic activity of seven metal alloys was studied by implanting solid rods of each alloy in the gluteal muscles of Sprague-Dawley rats which were sacrificed after twenty-four months. When the number of tumors in these rats was compared with the number in rats not operated on, in rats which had a sham operation, and in rats implanted with Silastic rods, no statistically significant differences in the incidences of the tumors in the several groups that was formed.

These animals that have been sacrificed and evaluated had their implant performed in the gluteal muscles. A new series of animals have been implanted where the implants were done onto the femurs of imbred albino Sprague-Dawley rats. Implants have been performed both in solid and in powder form of different average particle diameter. In addition, two groups of animals have been implanted at age 1 year rather than in the immature stage to define the incidence and occurrence of tumors in old animals. Controls and shams are included with these test groups.

Out of a total of 648 rats planned for this project, 472 have been implanted to date. The animals are to be sacrificed after 24 months (Table II).

XI. IN VIVO COUPLE CORROSION

The dog implanted 30 months ago with couple corrosion specimens has been sacrificed. The animal hosted the following specimens:

4, Cast Vitallium and Wrought Vitallium

4, Cast Vitallium and $MP_{35}N$

4, Cast Vitallium and Graphite

4, Cast Vitallium and Ti6Al4V

These implants consist of polished discs fastened together with a polyethylene rivet.

The corrosion specimens along with the surrounding soft tissue were removed, fixed in 6% Glutaraldehyde and stored cold in 50% alcohol until the implants were removed. Half the surrounding tissue will be processed for histology and the remainder embedded for electron microprobe analysis at Argonne. The couple corrosion implants will be evaluated by Dr. Rostoker.

XII. STUDIED OF METAL CONCENTRATIONS IN TISSUES

Electron microprobe investigations have been carried out on metal implants in bone. The metal implants included titanium fiber and Cr-Co-Ni-Mo alloy. The implants have remained in place for a period of two years before sectioning and analysis took place. With attention focused primarily on the Ti fiber, concentration profiles were measured at the metal-tissue interface. Many locations were examined and all showed similar characteristics. The maximum titanium concentration in the tissue adjacent to the fiber was some 0.6 w/o. The Ti concentration decreased in a regular fashion as one went further into the tissue, reaching background levels some 450-500 μm from the fiber interface. Simultaneous measurements of the calcium content in this

region indicated the presence of calcified tissue. Additional studies on other alloy implants are in progress.

XIII. HUMAN EXPERIMENTATION PROGRAM

Design and Manufacture of Prosthetic Devices

Design studies and manufacture of prototypes of segmental replacement has been accomplished. Particular emphasis has been placed in devices for replacement of segmental of the distal end of the femur and proximal end of the tibia as these cases represent probably over two-thirds of the instances encountering clinical practice where segmental replacements are necessary. A rolling pin type of design was chosen. Fiber metal composite coating was applied both in the intermedullary projections and at the level of the replacement segment. The devices for the distal end of the femur and proximal end of the tibia were made so as to provide for arthrodesis of the knee joint at the time of reconstruction. Plates and screws were also designed to provide an immediate fixation.

Patient Implantation (See enclosed manuscript, Appendix III)

Under this protocol four patients have been operated on.

Case I Fibrosarcoma of the tibia, left. Segmental replacement of distal tibia with arthrodesis of the knee joint. Patient ambulatory with full weight bearing and asymptomatic.

X-rays: Complete bridging across the defect.

Case II Giant cell tumor distal femur, left. Segmental replacement of distal femur with arthrodesis of the knee joint. Patient ambulatory with full weight bearing and asymptomatic.

X-rays: Complete bridging across the defect.

Case III Traumatic loss of distal femur. Segmental replacement of distal femur with arthrodesis of the knee joint. Patient ambulatory with full weight bearing and asymptomatic.

X-rays: Complete bridging across the defect.

Case IV Chondrosarcoma upper tibia. Segmental replacement of proximal and midshaft tibia. Patient ambulatory with weight bearing.

X-rays: Bridging across segment.

TABLE I

CURRENT BABOONS

SITE AND PROCEDURE	ANIMAL	TIME POST OP. (MO.)	POST PLATE REMOVAL (MO.)
Femur:			
Segment & Rod Fiber Metal	964R[1,3]	56	
	964L[2]	40	22
	1645R[2]	39	10
	2589[2]	38	11
Short Solid IM Rod	963R[2]	40	17
	1812R[2]	30	15
Solid Segment	410L	5	
Rolling Pin Design	1809	10	
	1643	13	
Long Solid Rod	410R	13	
Ground vs. Chip Graft	3048	4	
Tibia:			
Segment & Rod Fiber Metal	1645L[2,3]	44	10
	963L[2]	39	10
	1812L[2]	37	15
Humerus:			
Segment & Rod Fiber Metal	2547[2]	39	11
	902[3]	39	
	2588[2]	40	14

1 - No Graft

2 - Removal of Plate

3 - Secondary Graft

TABLE II

CARCINOGENESIS TEST GROUPS

TEST MATERIAL	SOLIDS	POWERS		
		-5μ	30-44μ	Wear Debris
Titanium	+	+	+	
Titanium implanted at age 1 year		+		
Ti6Al4V	+	+	+	
316L	+	+	+	
316L implanted at age 1 year		+		
Wrought Vitallum	+			
Cast Vitallium	+	+	+	
$MP_{35}N$	+		+	
Silastic	+			
PMM	+		+	
Hifax 1900	+			+
Delrin 150	+			+
Sham				
Sham performed at age 1 year				
Control				

27 groups (24 rats/group) = 648 rats

472 have been implanted to date

LEGENDS

FIGURE 1

Cross-section of baboon femur with segment 60 months after implantation. 6 x magnification. Note complete bone ingrowth. The plate was located at the lower left hand corner.

FIGURE 2

Section of the distal bone - fiber metal interface of a femoral replacement 60 months after implantation. 7 x magnification. Bone ingrowth can be seen in the rod and segment

FIGURE 3

Section of the proximal bone - fiber metal interface of a femoral replacement 60 months after implantation. 8 x magnification. Bone ingrowth can be seen in the rod and segment.

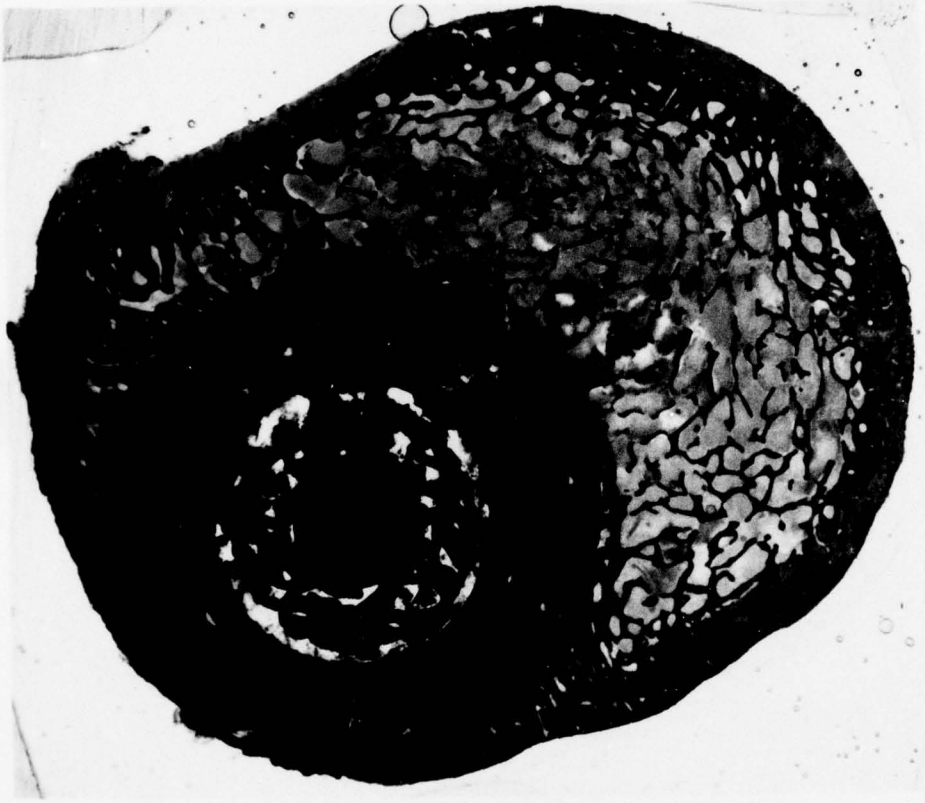

FIGURE I Cross-section of baboon femur with segment 60 months after implantation. 6 x magnification. Note complete bone ingrowth. The plate was located at the lower left hand corner.

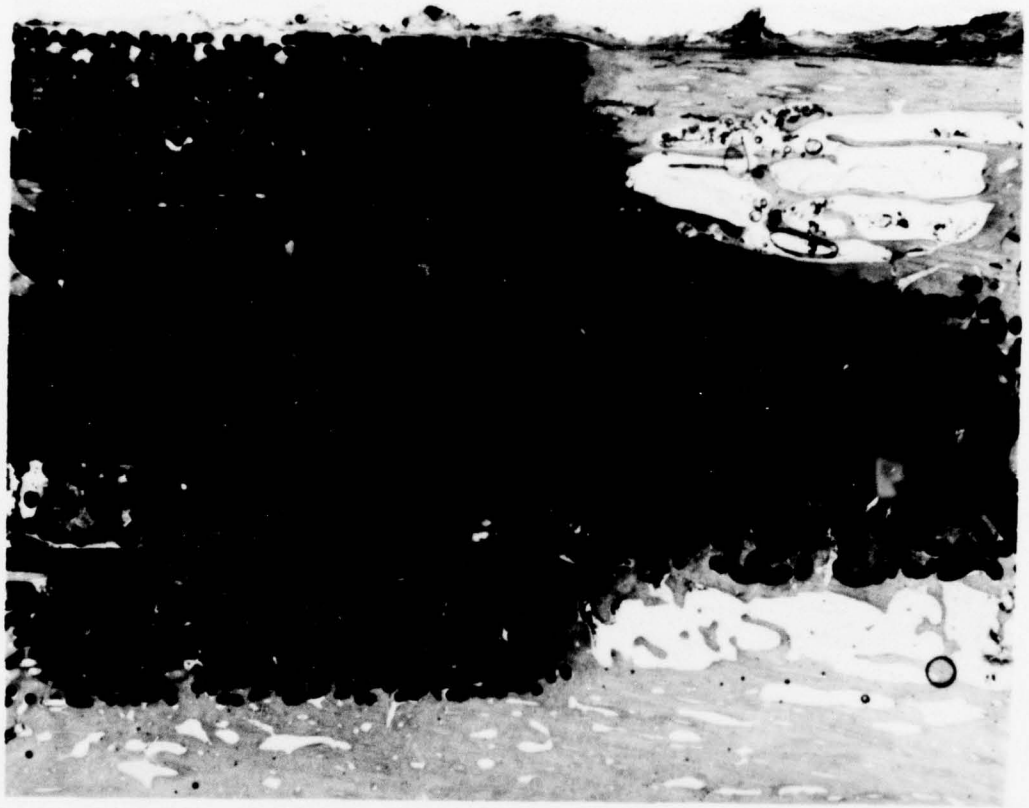

FIGURE 2 Section of the distal bone - fiber metal interface of a femoral replacement 60 months after implantation. 7 x magnification. Bone ingrowth can be seen in the rod and segment.

FIGURE 3 Section of the proximal bone - fiber metal interface of a femoral replacement 60 months after implantation. 8 x magnification. Bone ingrowth can be seen in the rod and segment.

APPENDIX I

PRELIMINARY MSS: Segmental Replacement of Bone Using a Fiber Metal Implant

by: Gunnar B.J. Andersson, Andre Gaechter, Jorge O. Galante, William Rostoker and Robert A. Miller

APPENDIX II

MSS SUBMITTED: Metal Carcinogenesis: A Study of the Carcinogenic Activity of Solid Metal Alloys in Rats

by: A. Gaechter, M. Alroy, G.B.J. Andersson, J. Galante, W. Rostoker, F. Schajowitz

APPENDIX III

MSS SUBMITTED: Segmental Replacement of Long Bones. Early Results in Five Patients.

by: J. Galante, W. Rostoker, G. Andersson, F. Sim

APPENDIX IV

XEROX COPY OF HUMAN EXPERIMENTATION PROGRAM - The use of Fiber Metals in Skeletal Reconstruction Following Radical Segmental Resection of Bone Tumors: Proposal for a Clinical Study. FROM PREVIOUS ARMY CONTRACT GRANT PROPOSAL

APPENDIX I

Segmental Replacement of Bone Using a Fiber Metal Implant

Gunnar B.J. Andersson, Andre Gaechter, Jorge O. Galante,

William Rostoker and Robert A. Miller

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INTRODUCTION

The fixation of implants to bone is a major problem in orthopedic surgery. While internal fixation devices are often attached with screws, pins or bolts, methylmethacrylate is preferred in total joint replacements; the acrylic polymerizes in situ and fills up the space between the implant and bone. Late loosening of implants has focused the interest on the interface problems. (Charnley, 1972; Homsy, et al., 1972; Willert, Ludwig and Semlitsch, 1974; Feith, 1975; Lindweer and Hoof, 1975; Linder, 1976). New methods of fixation have therefore been suggested. These include both osseointegration of solid implants (Branemark, et al., 1969) and the use of porous implants.

Bone ingrowth into the void spaces of a porous material could provide ideal skeletal fixation for permanent implants such as total joint prostheses or for prostheses used in the replacement of a bone segment lost because of disease, tumor or trauma.

Several authors have reported bone ingrowth in prostheses with porous surfaces of metallic, ceramic, polymeric and composite materials (1,2,3,8,9, 10,11,12,13,14,15,16,17,18,19,20). Adequate pore size, biological compatibility, intimate contact with the surrounding bone and good stability during the early period of bone ingrowth are pointed out as important requirements. The choice of the optimal porous material, particularly in relation to its mechanical properties and to problems associated with weight bearing, is still the subject of considerable discussion. Ideally, such a material should have adequate crack resistance, particularly under impact and a compliance comparable to bone. It should also be easily manufacturable to precise dimensions and as thick or thin coatings to a solid core. ( ).

A porous titanium fiber composite, manufactured by molding and sintering short length fibers, has been described in previous publications (4,5,6,7).

The fiber is disposed as a sleeve over a solid load bearing segment. Some of the mechanical and biological properties of the material, as reported previously, are summarized below.

The purpose of the present study was twofold; viz. to investigate the applicability of the material as a prosthesis for massive bone replacement, and to study the biological tissue reaction to the implant both in short term and long term perspective.

THE TITANIUM FIBER METAL COMPOSITE

Unalloyed, annealed titanium wire was converted to fiber form by first kinking it between meshing gears, and then cutting it into appropriate lengths. The kink pattern has a sinusoidal wave aspect with a wavelength greater than 0.25. This procedure increases the degree of interlock and the "green" strength, and minimizes parallelism between adjacent wires in the molded body. The wire diameter was 0.25 mm, and the wire was cut to lengths ranging from 1.9 to 3.8 cm. The wires were molded as units using constraining dies and moving punches. A sleeve type configuration of mold was used in a punch/core arrangement. The molding operation was followed by a sintering stage in which points of contact became actual metallurgical bonds. The manufacturing process has been described in detail previously (Galante & Rostoker, 1973). The diameter of the wire and the molding pressures were chosen to give a void content of about 50%. The pore shapes cannot be described in any simple geometrical shape, the largest being approximately equal to the wire diameter. The usual pore size is considerably greater than the 100μ found necessary by Hulbert, et al. (1969) to allow mineralized bone ingrowth. The pores are completely inter-connected so that bone can penetrate the entire body of the material (Galante, et al., 1971).

The mechanical properties of the material have been described by Galante

and Rostoker (1973), and Rostoker, Galante and Shen (1974). The elastic properties are more like an elastomer than a metal. The elastic modulus is about $10^4/cm^2$ for the strain range of about 1%. Because of its high compliance (large strains per unit applied stress) the composite provides for a load-distributing behavior.

Failure of the material does not occur by the propagation of cracks, because cracks do not form. Failure occurs as a tearing process by rupture of individual sintered bonds. During a tearing test in tension stresses in the order of 70-140 kg/cm^2 are reached before failure occurs.

Bone ingrowth into the fiber metal composite has been studied previously in animal models (Lueck, et al., 1969; Galante, et al., 1971; Lembert, et al., 1972; Galante & Rostoker, 1972, 1973). In the intramedullary canal of the proximal femur of dogs, new bone formation was observed in the periphery of the implant after two weeks, and bone ingrowth occurred into the void spaces after three weeks. At 12 weeks there was complete infiltration in 72% of the slides. The density of the implant and the intimate contact between implant and bone were both found to be important considerations. When the strength of the bone implant bond was studied using tensile tests in an Instron testing machine a positive correlation was found between the strength and the presence of bone in the periphery. The depth of the penetration of bone, on the other hand, was not found to be of significant importance. The mean shear strength recorded in these experiments was from 1.7 to 16.8 kg/m^2, which approximates the strength of normal trabecular bone. A change in pore size (from 190 to 390 μ) did not influence the shear strength.

MATERIAL AND METHODS

Forty-three segmental replacement prostheses were inserted into thirty-eight adult female papio-papio baboons. Thirty-four animals had one implant, three had two implants and one had three. Thirty-nine of the implants were

complete fiber metal implants, four were control prostheses, as described below. Twenty-one implants were replacements of femoral segments, thirteen of tibial and nine of humerus segments. Eleven fiber metal implants are in animals still alive. These were inserted thirty-five to fifty-three months prior to the final evaluation. In addition two of the control animals, evaluated at twelve months, are still alive. The other animals were sacrificed six to sixty months after surgery (Tables 2, 3).

The length of the replacement segments was 5 cm. for the humerus, 6.3 cm. for the tibia, and 7.6 cm. for the femur. The lengths were chosen as the longest which would still allow fixation of a plate on both sides of the implant using a compression fixation device. The replacement segment consisted of a solid Ti 6% Al 4% V tube onto which titanium fiber sleeves were sintered. The sleeves were fabricated as described earlier. For the tibia and femur the cross-sections were round, and dove-tails were molded at both ends of the segment to increase the rotational stability (Figure 1). For the humerus the cross-section was triangular. A central solid rod of RMI titanium alloy onto which unalloyed titanium fiber sleeves were sintered was used as an intramedullary rod (16.8 cm. long for the femur, 13.2 cm. for the tibia and humerus). This rod was inserted through the replacement segment to provide stability. Additional stability was provided by means of a Ti 6% Al 4% V semitubular plate and four stainless steel screws.

The control replacement segments were all of the femoral type, with the same dimensions as above. Two implants had fiber metal segments, and a solid Ti 6% Al 4% V intramedullary rod, two had fiber metal intramedullary rods and solid segments.

All surgery was performed under general anesthesia using standard surgical techniques. Prophylactic antibiotics were given routinely (Clindamycin). A lateral approach was used for the femur, antero-lateral approaches for the

humerus and tibia. The appropriate segment was resected using a reciprocating saw, and the segment fitted. The intramedullary rod was then threaded through the intramedullary canal, and through the segment. Following this the plate was applied in compression.

Three different surgical procedures were used. In seven femurs the resection was subperiosteal and no bone graft was added. In twelve an extraperiosteal resection was performed without simultaneous bone grafting (4 femurs, 5 tibias and 3 humeri). The other procedures were all extraperiosteal resections with autologous bone grafting using bone ships from the resected segment, i.e. mainly cortical bone (6 femurs, 8 tibias and 6 humeri).

The animals were housed in cages with inside dimensions of 74 x 89 x 117 cm. They were encouraged to use their limbs the day following surgery. Five to ten times a day the animals were stimulated to vigorous activity, such as jumping and swinging.

Thirty mg/kg body weight of oxytetracycline was given intravenously one month before sacrifice, and one week before sacrifice 40 mg/kg body weight chlorotetracycline was given intravenously in addition.

The plate was removed in eight of the eleven animals still alive, at five to fifteen months before the final evaluation.

Following sacrifice the entire implanted bone with surrounding soft tissue was removed as well as the lung, kidney, liver, spleen, pancreas and the regional lymph nodes. The segment was first evaluated macroscopically for areas covered and not covered by bone. Contact x-rays were then taken from each specimen and evaluated for union, interface contact and radiolucent areas. (Table 4). The segment and the intramedullary rod of each specimen were then cut in 5 to 10 horizontal slices (Figure 1). In addition, one vertical cut was made through the middle of the proximal and distal implant-bone interface. The sections were embedded undecalcified in polymethylmethacrylate.

Thin slices were cut with a diamond saw, ground down to 50 to 100 micron layers and stained with acid fuchsin. All sections were evaluated histologically and rated by a numerical system (Table 4). The evaluation was made separately for the intramedullary rod, the proximal and distal, flat bone replacement interfaces and the segment. For the rod and segment two to five sections of each were evaluated; bone ingrowth into the total surface area of all slides for each was considered a 100% contact.

RESULTS

No operative or postoperative complications were encountered in the experimental series. The animals all used their limbs the day following surgery, and within two weeks their behavior was the same as before surgery. When stimulated to activity no differences between the operated and not operated limb could be noted at that time or later.

Radiographic Evaluation

All replacement segments were radiographically intact. One rod was broken at the distal end, in a humerus with non-union. Uninterrupted bone formation across the segment was found in 15 of the extraperiosteally resected segments with bone transplantation (75%) and in five of the subperiosteally resected segments (71%) (Figure 2a). Non-union was present in two humeri and three tibias in which bone transplantation was performed, and in two subperiosteally resected femurs. None of the animals in which the bone was resected extraperiosteally without simultaneous bone transplantation obtained union. Average numerical values for the different groups are shown in Tables 5 and 6.

The bone-prosthesis interface evaluation was closely associated to the development of bone across the segment. For the grafted animals total interface contact was found in eleven of twelve femoral interfaces (92%), in eleven of twelve humerus interfaces (92%), and in eleven of sixteen tibia interfaces

(69%). The subperiosteally resected animals had a total interface contact at nine of fourteen interfaces (64%). In the non-grafted group (20 interfaces) there was only one interface with total contact (5%), seven with partial contact (35%).

The radiographic results of the control animals are shown in Table 7. In one animal uninterrupted bone formation was found across the prosthesis with partial interface contact. That prosthesis had a solid segment, but a fiber metal rod. In that animal, and in all control animals, radiolucent areas of considerable size were found around the prosthesis (Figure 2b). Such areas were found in none of the other animals.

The development of the bone bridge can be assessed over the evaluation periods: in the grafted animals at six months in two of six animals, at one year in all but one, and at two years in all animals.

In the eight animals in which the plates were removed no changes have been noted in subsequent x-rays, the animals being fully active and weight bearing.

Macroscopic evaluation

All plates were found intact at autopsy, one of the screws was broken. In all animals with bone bridging the segment radiographically, there was uninterrupted bone covering the segment, except under the plate, which was always separated from the segment by a thin soft tissue layer. All segments in which bone formation had not occurred across the prosthesis were covered with a similar soft tissue layer, tightly adherent to the fiber metal framework. No signs of infection or gross evidence of tissue intolerance was noticed. In two specimens, both unstable without bone bridging the segment, small amounts of black staining material was found in the soft tissues between the fiber metal and the plate, indicating wear due to motion between the components.

Histological evaluation

The histological results are summarized in Tables 5 and 6. Bone ingrowth into the fiber metal intramedullary rod was found in 26 of the 28 fiber metal prostheses (92%). These were both extraperiosteal resections without simultaneous bone transplantation. In 19 of these 26 implants (67% of all implants) bone growth was uninterrupted up to the solid core.

At the interfaces bone ingrowth was related to the surgical procedure, the implant site and to the implantation period. In the grafted animals bone ingrowth occurred in 17 of 22 interfaces (77%). The ingrowth was complete in 9 (41%). The corresponding figures for the subperiosteally resected femurs were ingrowth in 8 of 14 interfaces (57%), with complete ingrowth in 5 (36%). In the non-grafted, extraperiosteally resected segments, ingrowth was found in 6 of 20 interfaces (30%), with complete ingrowth in two only (10%).

In the grafted animals interface ingrowth was more frequent for femoral implants (100%, with complete union in 67%), than for tibial implants (70%, with complete union in 20%), and humerus implants (67%, with complete union in 50%).

The time of implantation had an obvious influence on the bone ingrowth. Thus, for the grafted animals bone ingrowth was found in eight of twelve interfaces at six months (17%), at later sacrifice periods in seven of eight (88%). Finally in the non-grafted animals ingrowth was only found in those sacrificed at twelve months or later.

Over the fiber metal segment bone ingrowth was irregular occurring in 10 of the 20 segment replacements that were bridged by bone. It was superficial in all but one segment.

The histological evaluation of the control segments showed complete bone ingrowth into the fiber metal intramedullary rod at 6 months. No bone ingrowth occurred at the interface or segments.

The bone growing into the fiber metal and the bone in the immediate surrounding of the prosthesis was mature, laminated, with intimate contact between the bone and the metal fibers (Figure 3, 4). No bone resorption was noted in the stable implants. No abnormal tissue reactions were seen surrounding the implants or in the organs removed.

The fluorescence-microscopic studies showed remodelling processes in the bone within the void spaces of the fiber metal implants, as well as in the surrounding bone.

By and large there was agreement between the radiographic and histologic appearance. At five interfaces, however, a good radiographic result was found where no bone ingrowth could be found histologically. In an effort to understand why in some cases bone ingrowth did not occur the initial (postoperative) x-rays were evaluated for bone-prosthesis contact. A gap between the prosthesis and bone exceeding 1 mm was found in 80% of the implants where interface bone ingrowth did not occur, compared to 20% in those in which bone ingrowth did occur.

DISCUSSION

The study shows that fiber metal prostheses can successfully be used to bridge large defects of long bones in primates under weight bearing conditions and that bone formation can occur over the prosthesis when autologous bone is grafted. This is not unique by itself because several other techniques have been devised to bridge extra-articular bone defects, including transplantation of autologous cancellous or cortical bone, usually supported by internal or external fixation, arthroplasty utilizing custom-made prosthesis, and transplantation of homogenous grafts (Wilson and Lance, 1965; Albrechtsson, 1971; Ottolenghi, 1972; Parrish, 1972; Tuli, 1972; Wilson, 1972; Enneking and Shirley, 1977). The differences between the procedure described here and these other techniques is the osseointegration of the prosthesis, and the

immediate weight bearing. The fact that no failure of the segment occurred shows that the strength of the structure was sufficient to withstand the load bearing stresses. Osseointegration is essential in the long term, however, because fatigue failures may occur as indicated by the rod fracture in the non-union humerus.

In addition to the information about the feasibility of the prosthesis for replacement, the experimental model gives information about the bone ingrowth in the composite. Bone formation occurred readily in the void spaces of the intramedullary rod. For the interface and the segment on the other hand, bone ingrowth was related to the surgical procedure. An intimate contact between bone and prosthesis at the interface seems essential to obtain good bone ingrowth. This confirms previous work by Cameron and colleagues (1976). As to the segment, it was necessary to transplant bone or to retain the periosteum to obtain a successful bone bridge. However, even then, bone ingrowth was unpredictable in the segment area, usually with a spotty distribution. A probable explanation for this is the bone transplantation technique. Due to its thin iliac crest cancellous bone is not readily available in the boboon. It was therefore accepted to use the mainly cortical bone of the segment, which was crushed in pieces. Under these circumstances it is difficult to obtain a close contact between the graft and the fiber metal composite.

The excellent bone ingrowth obtained in the intermedullary rod, and in the interface area is encouraging considering the possible use of the fiber metal composite in joint replacements. Bone ingrowth can occur in spite of the micromovements caused by weight bearing. Larger movements were prevented by the design of the prosthesis and the use of the bone plate. Although not investigated here it is probably essential to prevent such motion to allow bone formation in the void areas (Cameron, et al., 1973). When bone

ingrowth has occurred stability appears to be sufficient without the plate, as found in the eight animals still alive in which the plates were removed.

The biocompatibility of the system was excellent. This supports previous investigations of titanium implants (Brainmark, et al., 1969; Lundskog, 1972; Nilles, et al., 1974; Escalas, et al., 1976; Lennons, et al., 1976).

Table 1

Segmental replacement in animals still alive (11 implants). All resections were extraperiosteal and autologous bone grafting was performed. Compression fixation was noted.

Bone Segment Replaced	Autologous bone graft	Postop. Period (Months)	# of Implants
Femur	yes	~ 53	1
		~ 36	2
	yes	36	1
Tibia	yes	~ 41	1
		~ 35	2
Humerus	yes	~ 36	3
	no	36	1

TABLE 2

SEGMENTAL REPLACEMENT OF EXTRAPERIOSTEALLY RESECTED SEGMENTS.

Bone Segment Replaced	Autologous Bone Graft	Sacrifice Period	No. of Implants
Femur	Yes	6	2
		12	1
	No	6	1
		12	2
Tibia	Yes	6	2
		12	2
		18	1
	No	6	1
		12	2
		18	1
		24	1
Humerus	Yes	6	2
		12	1
	No	6	1
		12	1

TABLE 3

SEGMENTAL REPLACEMENT OF SUBPERIOSTEALLY RESECTED SEGMENTS OF FEMUR

Sacrifice Period	No. of Implants
6	3
12	2
33	1
60	1

TABLE 4

RADIOGRAPHIC AND HISTOLOGIC EVALUATION RATING

Radiographic Evaluation

Segment

0 = No bone formations or minimal bone formation at one or both ends of the segment.

1 = Bone formation at one or both ends with incomplete extension over the segment.

2 = Uninterrupted bone formation across the segment.

Interface

0 = No contact.

1 = Partial contact.

2 = Total contact.

Histologic Evaluation

0 = Non-union; fibrous tissue ingrowth or interposition.

1 = Partial union; limited bone ingrowth or bone ingrowth into less than 50% of the total histological surface area.

2 = Complete union; bone ingrowth up to solid core in the intramedullary rod, and more than 5 mm. into the segment, over more than 50% of the total histological surface area.

TABLE 5

RADIOGRAPHIC EVALUATION OF ANIMALS STILL ALIVE

Bone Segment Replaced	Months after Implantation	Bone-graft	No. of Implants	Radiographic evaluation		
				Segment	I1	I2
Femur	36	Yes	3	2	2	2
	53	No	1	0	1	1
Tibia	36	Yes	3	1.7	2	2
Humerus	36	Yes	3	2	2	1.7
	36	No	1	0	0	0

TABLE 6

HISTOLOGIC AND RADIOGRAPHIC EVALUATION OF THE SACRIFICED ANIMALS

Mean values are given according to the numerical rating system

Bone segment replaced	Sacrifice period (m)	No. of Implants	Histologic Evaluation				Radiographic Evaluation		
			Segment	I1	I2	Rod	Segment	I1	I2
Autologous Bone Graft									
Femur	6	2	1	1.5	1.5	2	2	1.5	2
Tibia		2	0.5	0.5	1	2	0.5	1.5	0.5
Humerus		2	0.5	1	0.5	2	1	2	2
Femur	12 - 18	1	1	2	2	2	2	2	2
Tibia		3	0.7	0.7	1.3	1.3	1.7	1.7	1.7
Humerus		1	1	2	2	2	2	2	2
No Bone Graft									
Femur	6	1	0	0	0	2	0	0	0
Tibia		1	0	0	0	0	0	1	1
Humerus		1	0	0	0	1	0	0	0
Femur	12 - 24	2	0.5	0	1	1	0.5	0.5	1
Tibia		4	0.25	0.25	0.75	1.25	0	0.5	1.5
Humerus		1	0	1	0	1	0	0	0
Subperiosteal Resection									
Femur	6	3	1	0.7	0	1.7	1.7	1	0.7
	12	2	1	1	1.5	2	1.5	2	2
	36	1	0	2	0	1	2	2	1
	60	1	1	2	2	2	2	2	2

lateral approach was used for the femur, antero-lateral approaches for the

TABLE 7

EVALUATION OF CONTROL REPLACEMENT PROSTHESES (FEMUR)

Type of prosthesis	Sacrifice period (m)	No. of Segments	Histologic Evaluation				Radiographic Evaluation		
			Segment	I1	I2	Rod	Segment	I1	I2
Solid segment/	6	1	--	0	0	2	0	0	0
Fiber metal rod	12	1	--	--	--	--	2	1	1
Fiber metal segment/	6	1	0	0	0	--	0	0	0
Solid rod	12	1	--	--	--	--	0	0	0

APPENDIX II

METAL CARCINOGENESIS

A STUDY OF THE CARCINOGENIC ACTIVITY OF SOLID METAL ALLOYS IN RATS

BY

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Metal Carcinogenesis

A Study of the Carcinogenic Activity of Solid Metal Alloys in Rats*

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ABSTRACT: **The carcinogenic activity of seven metallic alloys was studied by implanting solid rods of each alloy in the gluteal muscles of Sprague-Dawley rats which were killed after twenty-four months. When the number of tumors in these rats was compared with the numbers in rats not operated on, in rats which had a sham operation, and in rats implanted with Silastic rods, no statistically significant differences in the incidences of the tumors in the several groups were found.**

Metals, metallic alloys, and polymers are being implanted in the human body with increasing frequency. It was estimated, for example, that approximately 1,000 total hip arthroplasties are performed every day all over the world[6]. Only a few reports described tumors associated with surgical implants in humans[4,5,9] or in animals[2,7,13]. However, the introduction of new implant materials and the younger age of patients being treated raise serious concern about possible carcinogenic hazards.

Most of our knowledge concerning the possible carcinogenicity of implanted materials comes from animal studies. These studies showed that not only is the chemical reactivity of the implanted materials important but also their physical characteristics, geometry, and surface texture[3,10]. Certain compounds containing beryllium, cadmium, chromium, cobalt, iron, lead, nickel, selenium, zinc, and titanium appear to be carcinogenic in experimental animals[14], as do many plastics[11]. However, there have been only a few animal studies of the carcinogenic hazards of the metallic alloys commonly used for surgical implants. Heath and associates induced sarcomas in rats when cobalt-chromium-molybdenum wear products from total joint-replacement prostheses were implanted in muscle, and suggested that there is need for further careful investigation into the possible hazards of such wear products[15]. Other alloys are also used extensively with little knowledge of their carcinogenic potential.

The purpose of this investigation was to study the carcinogenic potential of several metallic alloys, currently in use for human implants, after implantation in muscle in rats.

Materials and Methods

Sprague-Dawley albino inbred rats (Charles River Breeding) were used for implantation. They were housed in polycarbonate cages (49.5 centimeters long, 26.7 centimeters wide, and 16.5 centimeters deep) with stainless-steel tops. A maximum of three animals of the same sex were housed in each cage. Processed pine shavings (Pin-Dri Lab Products, Garfield, New Jersey) were used as bedding material. Standard food (Purina Rat Chow) and fresh water were freely available. Six months after implantation, tetracycline hydrochloride (twenty milligrams per 100 milliliters) was added to the drinking water because the animals were plagued by pulmonary infections (*Bordetella bronchiseptica*).

Each rat was labeled using an ear-punching code at the time of implantation. Daily checks were made by the attendant, and every three weeks the animals were weighed and individually evaluated. Animals that did not survive the first six months, lost their implant, or lost their earcode due to bites were excluded from the study. Of the initial 310 animals, 260 were included in the study. A two-year experimental period was planned, but rats seriously affected by tumors before that date were killed and evaluated.

Seven metal alloys (Table I), all currently used for prostheses and internal fixation in humans, each were implanted in a separate group of rats. In addition, there were three control groups of rats: one with no surgery, one in which a sham operation was performed, and one in which Silastic was implanted.

All test coupons consisted of polished rods 1.6 millimeters in diameter and eight millimeters long, with rounded edges. The specimens were fabricated and their surfaces were polished and cleaned as required in the ASTM specifications for metallic surgical implants[1].

Each type of test coupon was implanted in the gluteal muscle mass of fifteen female and fifteen male rats except for the stainless-steel (316 L) coupons, which were implanted in twenty males and twenty females. The control groups consisted of fifteen females and fifteen males. The ages of the rats at the time of surgery ranged from twenty to thirty days and their weights, from seventy-five to 150 grams. Surgery was performed under general anesthesia with intraperitoneal Nembutal (pentobarbital) and the

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muscle and skin were closed with 4-0 chromic catgut sutures.

The animals were killed with an overdose of chloroform and complete necropsy (excluding skull and brain) was performed on all of them. All tumors seen macroscopically were photographed *in situ*, removed, and fixed in 10 per cent buffered formalin. The following organs were removed routinely and processed for histological evaluation: thyroid with larynx, lung, liver, spleen, pancreas, kidney, adrenal glands, and ovaries or testes. Each implant with the surrounding tissue was examined histologically. In the sham group the incised muscle was removed for histological examination.

Formalin-fixed tissues were embedded in paraffin and sections five to seven micrometers thick were prepared and stained with hematoxylin and eosin routinely, and with van Gieson, periodic acid-Schiff, and Giemsa stains when necessary for diagnostic purposes.

Roentgenograms were made of sixty animals (eighteen months old or more) selected randomly from all groups, to exclude skeletal tumors. Only masses showing neoplasia were classified as tumors. Granulation tissue from injuries, bites, and the like were classified as such. Statistical analysis was performed using the chi square test.

TABLE I

METAL IMPLANT MATERIALS

Alloy or Trade Name	Composition*		Manufacturer
Stainless steel 316 L	0.02C, 0.47 Mn, 0.01 P, 0.003 S, 0.46 Si, 17.2 Cr, 13.77 Ni, 2.46 Mo, 0.24 Cu, 0.11 Co, Bal Fe.	†	Joslyn Stainless Steel Co., Indiana
Wrought Vitallium	19-20 Cr, 14-16 W, 9-11 Ni, 0.15 C max., 2 Mg max., 1 Si max., 3 Fe max., Bal Co	‡	Howmedica, Rutherford, New Jersey
Cast Vitallium	27-30 Cr, 5-7 Mo, 2.5 Ni max., 0.2-0.3 C max., 1 Mg max., 1 Si max., 0.75 Fe max., Bal Co	‡	Howmedica, Rutherford, New Jersey
RMI	3 Al, 8 V, 6 Cr, 4 Mo, 4 Zr, Bal Ti	‡	Alloy Specialties, Garden Grove, California
Unalloyed titanium	0.0009 C, 0.286 Fe, 0.030 Ox, 0.10 N, 0.0014 H, Bal Ti	†	Astro Metallurgical, Wooster, Ohio
$MP_{35}N$	C 0.025 max., Cr 19-21, Fe 1.0 max., Mn 0.15 max., Mo 9.5-10.5, Ni 33.0-37.0, P 0.015 max., S 0.0015 max., Si 0.15 max., Ti 0.65-1.0, Bal Co	‡	Latrobe Steel Co., Latrobe, Pennsylvania
Titanium 6 Al-4V	0.032 C, 0.17 Fe, 6.32 Al, 4.23 V, Bal Ti	†	Astro Metallurgical, Wooster, Ohio

* Composition in percentages by weight.
† Analysis supplied by manufacturer.
‡ Specification.

Results

No organ showed histological changes that could be related to a toxic effect. Tumors were found in sixty-seven of the 260 rats finally evaluated. Forty-eight rats had one or more benign tumors and nineteen had malignant tumors, twelve without and seven with metastatic lesions. The tumors without metastasis were four adenocarcinomas of the breast, three squamous-cell carcinomas, and one each of the following: adenocarcinoma of the rectum, mesothelioma, poorly differentiated carcinoma of unknown origin, schwannoma, and rhabdomyosarcoma. The tumors with metastasis included two mesotheliomas, two instances of malignant myeloproliferative disease, and one case each of reticulum-cell sarcoma, lymphoma, and malignant histiocytoma.

Of the nineteen malignant tumors, thirteen were in animals implanted with metallic alloys, two in animals implanted with Silastic, three in the control group not operated on, and one in the sham-operation group (Table II). Only one tumor appeared in a rat younger than fourteen months old.

There were no statistically significant differences between the incidences of tumors in each of the implant groups, in the Silastic group, and in the sham group ($p > 0.95$). There were also no differences in the incidence of tumors in males and females.

None of the tumors (malignant or benign) originated

TABLE II

MALIGNANT TUMORS FOUND AT AUTOPSY

Implant Material	No. of Rats Autopsied	No. of Tumors without Metastasis	No. of Tumors with Metastasis
Stainless steel	34	3	1
Wrought Vitallium	27	1	1
Cast Vitallium	22	—	—
RMI	22	2	—
Unalloyed titanium	24	1	—
Ti 6 Al-4V	22	—	1
$MP_{35}N$	30	1	2
Silastic	28	1	1
No implant	25	3	—
Sham operation	26	—	1
Total		12	7

at the site of the implant, and no inflammatory reactions were observed in these areas. A delicate collagenous capsule was always found surrounding the implant and the histological pattern of this layer was comparable for the different materials.

Discussion

The results of this study show that solid implants of seven different metallic alloys commonly used in orthopaedic surgery do not constitute a major carcinogenic hazard when implanted in the muscles of rats. This is an encouraging finding, but must not be taken to suggest that no carcinogenic effects can exist when the same alloys are used in humans. Clinical reports have indicated that tumors occur only after a considerable period of time [4,5,9,12]. The induction time in rodents is certainly much shorter, but no evidence is available to substantiate that two years in rats corresponds to the often-quoted "thirty to fifty-year latent period" for humans [11]. The average life span of Sprague-Dawley rats is between twenty and thirty months.

As mentioned previously, the physical characteristics of implants have been found to be important [3,10]. A rod shape was chosen here since a previous study showed that rod-shaped implants cause a greater tissue reaction than disc-shaped ones [16]. Human implants exist in many different shapes. Although they are usually solid when implanted, wear particles are produced which have a much larger ratio of surface area to unit mass. These particles may constitute an increased carcinogenic hazard, as suggested by Heath and co-workers and by Swanson and associates.

Muscle tissue has been used as the host for implants almost exclusively in studies of metal carcinogenesis. Bone, to which the human orthopaedic implants are applied, is a biologically different tissue, which may or may not respond differently.

Clinical studies have, as a rule, disclosed corrosion in the metal implants adjacent to the tumors. Electrolytic reactions of dissimilar metals in contact are believed to have contributed greatly to the neoplastic response. Although this study cannot shed any light on that problem, it is obvious that such risks may prevail and should not be taken lightly.

Although our results must be interpreted with these reservations in mind, the outcome of this study is reassuring. Careful follow-up of clinical experiences is essential to gain further knowledge of the carcinogenic hazards of metallic implants and the induction time of tumors in humans.

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APPENDIX III

SEGMENTAL REPLACEMENT OF LONG BONES. EARLY RESULTS IN FIVE PATIENTS.

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ABSTRACT

Large segments of long bone, resected because of tumor or trauma, were successfully replaced with prostheses made of a porous titanium composite supplemented by autologous bone grafts.

Early results in five subjects were reported. Radiographic evaluation showed bone extending over the prosthetic device in all cases. In one patient this was verified at operation, and in one at autopsy, when the patient died from a non-associated disease. Bone formation into the void spaces of the composite was confirmed histologically in that patient without evidence of tissue reaction. The clinical experience parallels that previously observed in animals.

INTRODUCTION

Segmental defects in long bones caused by disease or trauma can result in shortening, deformity and severe disability. When large segments are lost, autologous transplantation alone is not suitable as a method of reconstruction and the surgeon may have to use a prosthetic device or revert to amputation. Homologous transplantation from cadaveric bone is another alternative, but at the present time the procedure is still experimental (Mankin, 1976).

We suggest that replacements of major segments of long bones can be successfully carried out using a titanium fiber prosthesis supplemented with autologous bone grafts. This concept was derived from a series of long-term animal experiments in which major segmental resections were reconstructed by this method (Galante and Rostoker, 1973; Gaechter et al. 1976; Miller et al, 1976). Union between the implant and bone was obtained and the fiber metal segment was covered by a layer of uninterrupted living bone extending from the proximal to the distal part of the resected bone.

The purpose of this paper is to report the early results observed in a series of five patients who underwent segmental replacement for severe bone loss secondary to trauma or resection for tumors.

METHODS

The technical details and mechanical properties of the porous titanium fiber composite used have been described in detail previously (Galante and Rostoker, 1973). The replacement prostheses consisted of solid Ti 6% Al 4% V rods on to which titanium fiber sleeves were sintered. They were made after x-ray measurements to

fit the individual patient. A rolling pin design was adopted with a central replacement segment and distal and proximal projections designed to be inserted into the intramedullary canal or into matching drill holes in cancellous bone. Early fixation was obtained by means of Ti 6% Al 4% V plates attached to the bone by stainless steel or titanium screws using compression techniques. In one of the patients methylmethacrylate was used to obtain additional fixation of the intramedullary pins. Autologous iliac bone grafts were used routinely. In three of these patients the prosthetic device was used to arthrodese the knee joint.

Case Histories

Case #1 - A 62 year old female fractured her right tibia on September 21, 1975 after sustaining minor trauma. X-rays revealed a pathological fracture (Figure 1). Further investigation disclosed a diagnosis of metastatic endometrial carcinoma. No other metastasis were discovered. In October, 1975 a 9.5 cm segment was removed from the right tibia and replaced by a fiber titanium implant. As the distal resection line of the segment was near the ankle joint, the prosthesis was anchored with bone cement in the intramedullary canal to provide additional initial fixation. Plate and screws were applied and iliac bone grafting was completed. Histology showed the lesion to be adenocarcinoma with squamous metaplasia. The patient was treated postoperatively with pelvic radiation (5300 rads) for her primary endometrial carcinoma. She was discharged on November 25 with the leg immobilized in a PTB plaster cast. On December 3 the plaster cast was removed and a cast brace was utilized with partial weight bearing.

The brace was removed on May 5 at which time the patient was full weight bearing and walking without supports and without a limp. There was no pain and the range of motion of the ankle joint was only slightly impaired. X-rays showed complete bridging of the segment without radiolucent areas. On July 8, 1976 the patient died suddenly due to myocardial infarction. Post mortem examination of the tibia showed complete bridging of the replacement segment by bone and x-rays revealed close contact between implant and bone (Figure 2). The thickness of the covering bone varied from 1 to 5 mm.

Histologically, new bone formation was observed around the prosthesis. Some bone trabeculas were also seen between the fibers of the implant, particularly at the prosthesis-bone interfaces proximally and distally (Figure 3).

Case #2 - 56 year old laborer who developed a mass in the posterior aspect of the distal right thigh in January 1971. An open biopsy was carried out by his referring physician on 3/21/72 and he was referred to the Mayo Clinic for definitive treatment. Examination revealed a firm 4 by 2 cm movable mass in the posterior aspect of his distal right thigh. His general examination was within normal limits. Staging procedures revealed no evidence of metastatic disease. X-rays revealed a calcified irregular mass in the posterior lower right thigh. Tissue from the previous biopsy was reviewed and revealed a malignant fibrous histiocytoma. On 3/27/72 a radial en bloc resection was performed. His postoperative recovery was uneventful. More than three years later, however, the patient developed a metastatic lesion in the left upper lobe and on 6/20/75 a thoracotomy and wedge resection of the

metastatic lesion was performed. Recovery was excellent and the patient remained asymptomatic until nine months later when he returned complaining of aching discomfort in the right thigh. X-rays showed a solitary osseous lesion involving the distal right femur (Figure 4). Re-evaluation revealed no other evidence of metastatic disease. On 3/12/76 a segmental resection of the osseous lesion was carried out. This involved 12.5 cm of the right distal femur. The integrity of the bone was restored with a fiber metal prosthesis and iliac bone grafting. His postoperative course was excellent and primary wound healing was obtained. Ten days later a cast brace was applied with polycentric knee hinges. He was dismissed from the hospital two weeks postoperatively. When seen again six weeks later the patient was noted to be active and he had no discomfort. He had 30^{o} of knee flexion. X-rays showed early maturation of the iliac bone grafts (Figure 5). At that time, his cast brace was changed and he was dismissed home. Unfortunately, one month later the patient developed GI distress and died of GI hemorrhage. No autopsy was performed.

Case #3 - A 28 year old previously healthy male who in October 1975 experienced sharp pain in the right medial aspect of his tibia after physical exercise. The pain subsequently disappeared but re-appeared on January 20 when an x-ray showed a lytic lesion in the left tibial condyle. A biopsy revealed a diagnosis of fibrosarcoma. Surgery with excision of a 10 cm long segment of the tibia including the tumor was performed on January 29. The defect was temporarily filled with acrylic cement. The leg was placed in a plaster cast and the patient was then referred to us for possible reconstruction. On March 31, 1976

a 12.5 cm long fiber titanium prosthesis was used to replace the resected segment and arthrodese the knee joint. Because of difficulties to close the skin, bone grafting could only be done medially, laterally and posteriorly. A cylinder cast was applied and the patient was discharged on April 13. The patient was re-admitted on August 28 for iliac bone grafting anteriorly. During surgery solid bone formation and bridging from the femur to the tibia was observed over the posterior, lateral and medial aspect of the fiber implant. Histology of bone removed at the time of surgery disclosed viable bone overlying the prosthetic device. The patient is at present ambulating with full weight bearing.

Case #4 - A 30 year old male farmer complained of pain over the left knee after a fall in 1975. X-rays obtained in February 1976 showed a large lytic lesion involving the distal end of the left femur (Figure 6). A trocar biopsy was performed and a diagnosis of giant cell tumor was made. On April 20 the distal 10 cm of femur were resected and replaced by a fiber titanium implant which extended over the knee joint. Autologous bone from both posterior iliac crests was added and a plaster cast cylinder applied. The cast was changed for a cast brace on June 15. X-rays in September 1976 shows bridging of the prosthesis with bone (Figure 7). The patient is presently asymptomatic and full weight bearing without supports.

Case #5 - A 32 year old male who was involved in a car accident in July 1976 where he sustained a severely comminuted compound fracture involving the distal end of his left femur. At the time of initial debridement excision of the involved 12 cm of the distal left femur was required

because of marked comminution and massive contamination of the wound. The patient was then placed in skeletal traction for two weeks and a split thickness graft was used to provide complete coverage to the anterior portion of the wound. He was referred to us six weeks after his surgery for further reconstruction immobilized in a long leg cast. His wound was completely healed without evidence of infection. X-rays showed a complete loss of the distal 12.5 cm of the femur. Severe shortening amounting to 6 cm had occurred. After admission the cast was removed and skeletal traction was instituted. In 10 days, the original length was restored. On September 23, 1976 segmental replacement of the left distal femur with arthrodesis of the knee joint was carried out. Autologous bone grafting from both posterior iliac crests was performed. The patient did well postoperatively and is at present ambulatory with a long leg brace.

DISCUSSION

The early results reported on in this paper are encouraging. Prosthetic devices made of titanium fiber composites can function in humans under weight bearing conditions. The biocompatibility appear to be satisfactory; no adverse response had been noticed clinically, radiographically, or in histologic evaluation. This confirms the experience obtained in previous animal studies. The operative procedures were comparatively simple. Good initial stability, which is believed to be important to accomplish successful bone ingrowth and bone bridging, could easily be obtained (Gaechter et al., 1976). The length of the fiber metal segment and the medullary projections are important to ensure such stability, as also the application of the

plate in compression. In one patient the distal bone fragment was very small. It was felt at surgery that the plate alone might not provide adequate stability. Consequently, methylmethacrylate was used. The use of acrylic cement, however, should be avoided when possible as it prevents bone ingrowth into the intramedullary parts of the fiber composite. Animal experience has shown that bone formation into the intramedullary rod in every instance provided a crucial source of long term stability to the system. Following the experience in animals massive bone grafts from both posterior iliac crest have been used. Sufficient bone to cover the entire length of the resected segment was obtained in every instance.

One operative problem encountered was difficulty to close the skin over the transplanted bone in cases where resection of the segment had been done in a previous operation. It may be necessary, as in one of our patients, to complete bone grafting in a secondary operation. It is advantageous, however, to excise the diseased bone and insert the prosthesis at the same time. When the operation is carefully planned it does not prolong the procedure unreasonably. Further, shortening is prevented, and scarring and retraction of the skin and tissues making closure difficult does not occur. Should for some reason the implantation of the prosthetic device be delayed, length should be retained by either inserting a temporary prosthesis, to serve as a spacer, or by the use of extraskeletal fixation. In one of the patients, considerable length loss had occurred and treatment of traction for 10 days was necessary to regain normal leg length.

Lesions of the distal femur and proximal tibia probably constitute the most common indications for this type of procedure. It was chosen in these patients to arthrodese the knee joint across the fiber titanium

prosthesis. Alternative procedures such as replacement with knee arthroplastics can be considered. The patients operated on so far, however, were all comparatively young and very active and the long-term results of such a procedure therefore in question.

Radiography and histology indicate that the bone grafts quickly consolidate around the prosthesis. The continuity of the bone is thus restored, and hopefully long-term stability is ensured and the risk of loosening minimized. Further evaluation of patients will ultimately determine the role of the procedure is reconstructive surgery.

LEGENDS TO FIGURES

FIGURE 1 — Case #1. Radiograph shows pathological fracture (arrows) through metastasis in the right tibia.

FIGURE 2 — Post mortem contact radiograph of the right distal tibia with titanium fiber metal implant. The prosthesis is surrounded by bone.

FIGURE 3 — Photo micrograph of bone prosthesis interface showing bone from the periphery penetrating into the fiber titanium composite. (1) denotes metal fiber, (2) denotes bone.

FIGURE 4 — Case #3. Radiograph shows solitary osseous lesion involving the distal right femur.

FIGURE 5 — Radiograph of implant with surrounding bone graft.

FIGURE 6 — Case #4. Radiograph showing a large lytic lesion involving the distal end of the left femur.

FIGURE 7 — Radiograph of implant 5 months after surgery. Notice bridging of prosthesis with bone.

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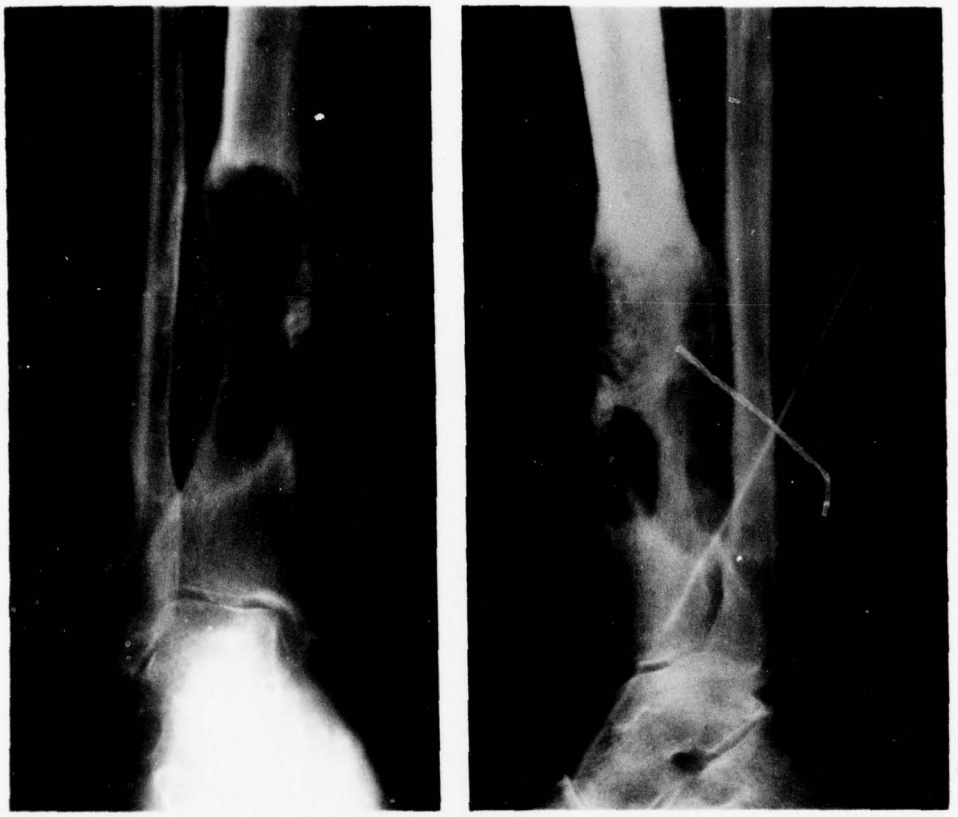
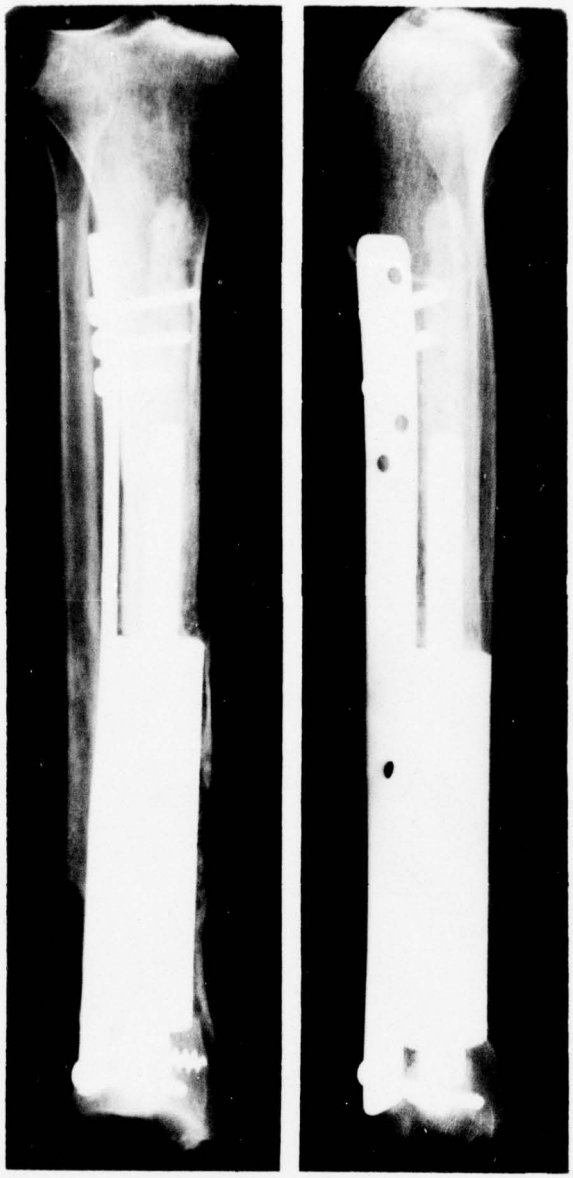


FIGURE 1



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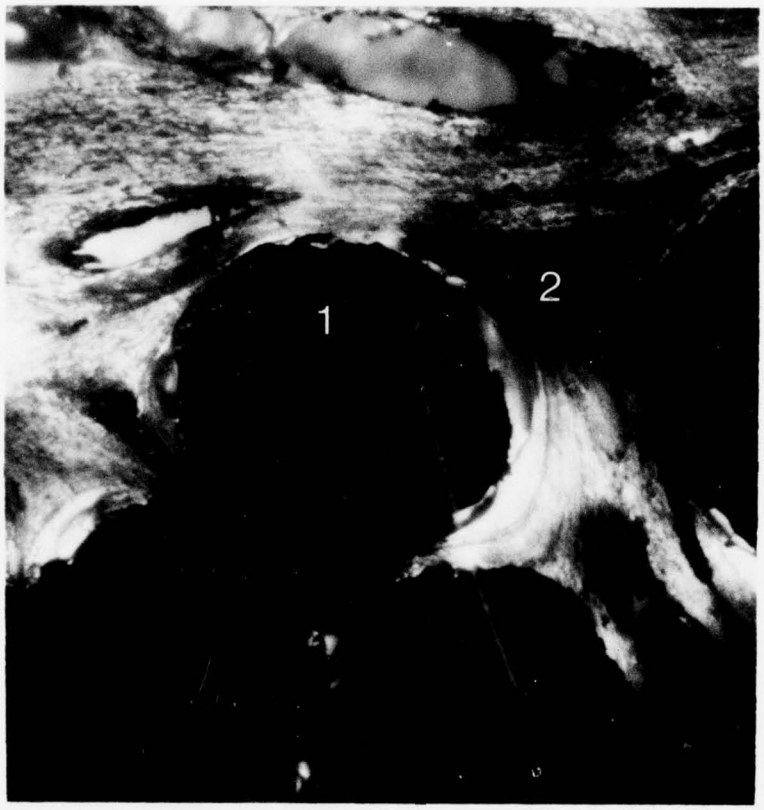

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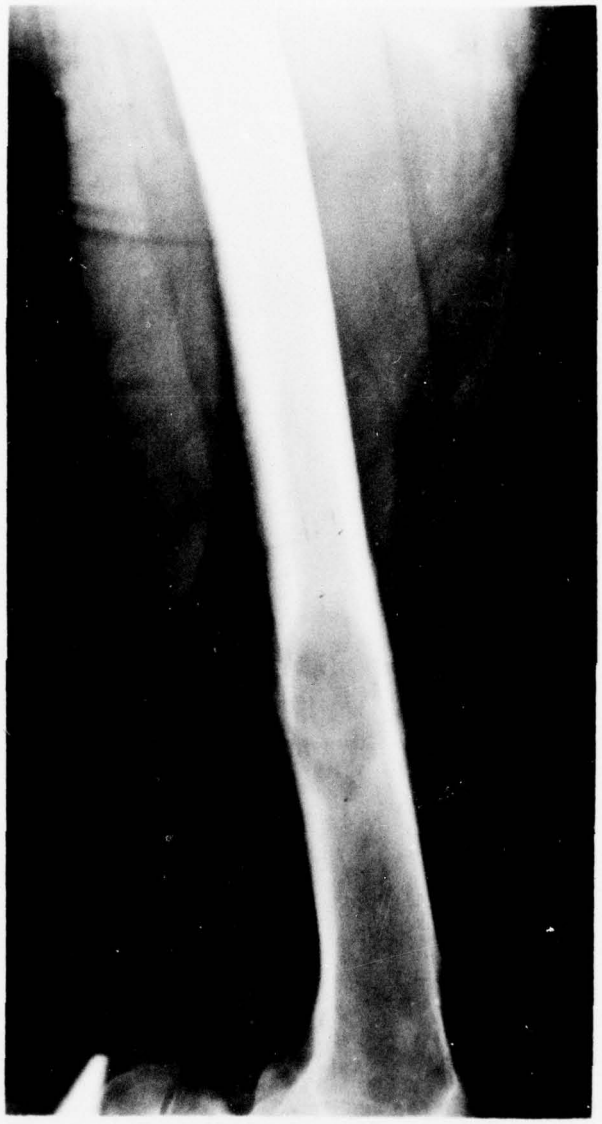

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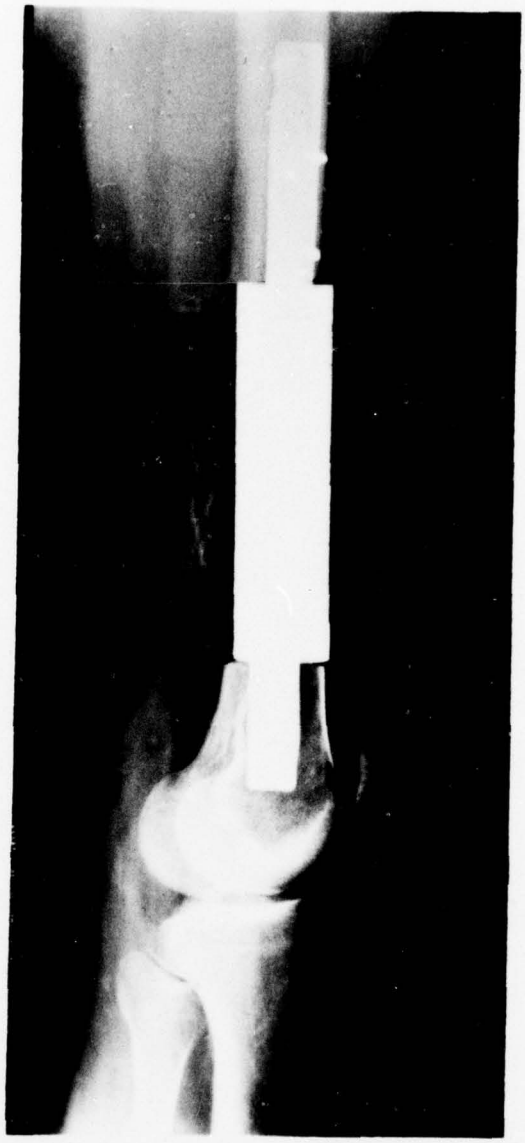

FIGURE 5

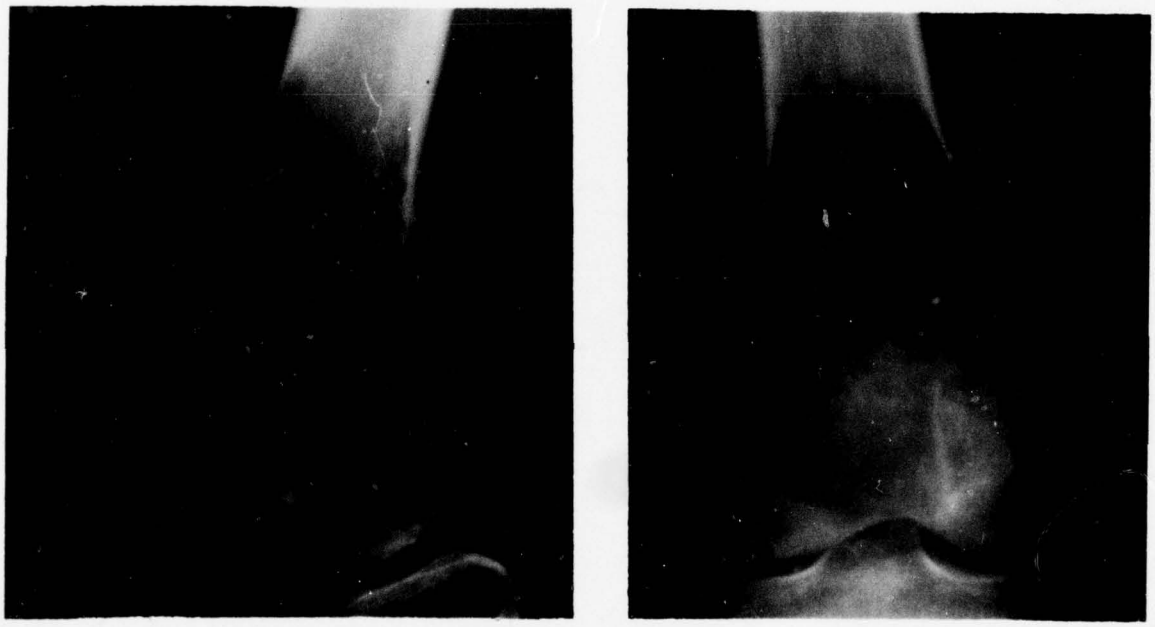

FIGURE 6

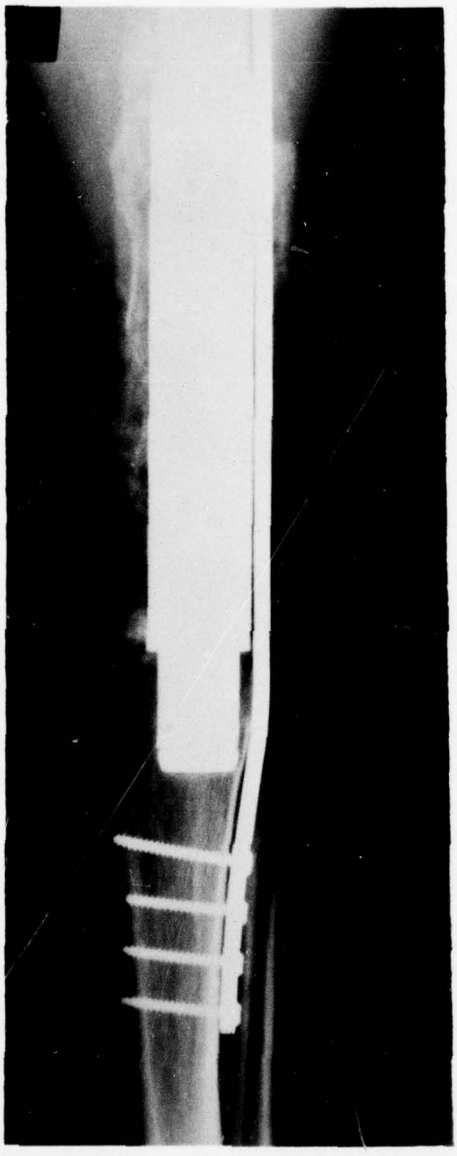

FIGURE 7

APPENDIX IV

HUMAN EXPERIMENTATION PROGRAM - The Use of Fiber Metals in Skeletal Reconstruction Following Radical Segmental Resection of Bone Tumors: Proposal for a Clinical Study

The success incurred up-to-date in animal experimentation with a segmental replacement prosthesis has prompted us to look into the possibility of clinical investigation for two reasons. One is the potential offer to patients for reconstruction with the fiber titanium prosthetic system. The second one is the possibility of using the system in a patient population on whom on the one side no other form of therapy will be available, and on the other side the same well-controlled human experiment could be provided.

Orthopedic oncology is a branch of orthopedics which demands unusual requirements in reconstructive measures. A primary bone tumor confronts the surgeon with the problem of not only eradication of the tumor, but also restoration of function in the extremity. Depending on the nature of the tumor, its location, and size, amputation may be necessary. However, a wide variety of osseous lesions involving the long bones, with or without involvement of the adjacent joint, are amenable to radical en bloc segmental resection (11,12). In addition, current research indicates that malignant lesions such as osteogenic sarcoma may be resectable with the use of current chemotherapy. Previously, however, even if the first goal of segmental resection of an osseous lesion was possible, the means available to restore the integrity of bone in the resected area were inadequate. Little interest was demonstrated in this form of treatment despite its limb-saving potential. However, with recent advances in reconstructive orthopedic surgery utilizing modern joint implants, we now have an effective means to restore the osseous integrity of the resected segment of bone (13). It is anticipated that

fiber-metal implants will be an effective scaffold for bone induction of iliac autogenous grafts to replace the segmental loss of bone. The procedure consists of:

a) Removal of an appropriate segment of affected bone, leaving intact the muscles, vessels, nerves and tendons that surround the bone unless they too are affected by the underlying tumor, in which case they must also be removed.

b) Replacement of the segment of bone with a specially designed prosthetic segment. This segment is made of standard orthopedic materials, but the design is new. The segment has been tested in laboratory animals with good results, but has not yet been proven in humans.

c) Fixation of the segment with a compression apparatus and inclusion of autogenous iliac bone graft, methylmethacrylate for additional immediate fixation.

d) Appropriate post-operative immobilization.

e) The segment is designed to become incorporated into bone, and therefore removal is not anticipated. It should be assumed that the segment will be left in place.

Background

It has been well shown that trabecular bone can be made to grow into porous materials (1,2,3,4), and that pore size is important (5,6). Research and development of a sintered fiber-metal skeletal implant has been underway in our laboratory for five years. This work resulted in the selection of a sintered titantium wire aggregate of specific confirguration and density as the material of choice, based on strength and measurements and histological studies. Deep penetration of the fiber metal by bone occurs rapidly,

intimate bone-fiber contact is established, and bond strength between bone and implant rapidly exceeds the shear strength of cancellous bone itself. Furthermore, results indicated that porous sintered fiber-metal composites achieve a strength of fixation similar to methylmethacrylate, and that the compliance of the fiber-metal bone complex is practically identical to that in bone alone, thereby avoiding the poor distribution of load with high stresses at contact points inherent in other methods of fixation (9).

Design of the final segmental replacement implant which is being tested extensively in animals consisted of an intramedullary rod made up of a solid core 2 mm in diameter surrounded by cylinders of sintered fiber metal. Larger fiber-metal cylinders fitted over a solid metal cylinder and corresponding to the length of diaphysis to be replaced are fitted over the rod, and the composite device is held in place with a profiled compression plate.

Material

The segmental replacement in a long bone as proposed is made possible by the discovery and exploitation by the authors of a class of materials which are singularly compatible with live bone under load-bearing circumstances. A porous metal has been developed which permits invasion of its pores by calcified tissue and vascular elements such that the result is a composite of the living synthetic.

At the same time the porous material can be incorporated with very strong load-sustaining components which prevent the composites from featuring and permit load transfer. With this concept, whose feasibility has been demonstrated, we expect the long bone to remodel such that the bone fragments and the segment prosthesis become integral. A prosthetic

device of this nature would eventually become incorporated into the skeletal structure of the host. However, until such time as bone ingrowth occurs, rigid stability between the implant is essential.

This porous metal is manufactured by molding short lengths of fine fibers or wires of metal into precise shapes and bonding the fibers to each other by a sintering thermal treatment. The resultant parts have precision shapes and dimensions and may be assembled by mechanical attachment or welding into implants containing solid or tubular elements.

The modeled and sintered fiber has unique attributes. There is about 50% void in the form of interconnecting channels with principal dimensions of the order of 100 microns. Thus it is possible for calcified tissue and vascular elements to enter the external surface and penetrate throughout the bulk of the metallic material. Unlike most porous materials, this sintered body is not brittle. It can deform and can sustain substantial impact forces. It cannot fracture in the normal sense of the term. In fact, under extreme distortion it can tear as would a fabric. The material has remarkable elastic properties, which are closely similar to trabecular bone.

Implant Design

The implant constitutes a tubular element equivalent in length to the defect and structurally representing the cortical construction of the long bone. Such custom implants will be provided by the Orthopedic Research Laboratory.

In each case the prosthesis is a tubular configuration composed of a strong and stiff thin-walled tube over which a contiguous assembly of thick-walled sleeves of porous molded fiber are disposed. The assembled prosthesis has the aspect of a porous body in which the pores run in all directions, radially and longitudinally.

The sleeves of moded porous fiber are dove-tailed to each other. The sleeves at each extremity are dove-tailed also with the intent to lock to a matching profile created in the ends of the live bone fragments by surgical procedure. The sleeves at each extremity are also molded and sintered so as to be extremely deformable. In this way when the fragments and the prosthesis are pulled together, the porous fiber material deforms to achieve complete conformal interface with the end faces of the bone fragments. This is absolutely necessary to achieve longitudinal bone ingrowth and attachment to the prosthesis. This is also the factor which distinguishes this porous material from others proposed for similar applications.

For long-term load-bearing, the cortical prosthesis is combined with an intramedullary nail. A third component of the prosthesis system is a plate which provides immediate fixation by means of four screws and a compression device which is removed after at least two screws are applied. The plate could be removed at some later date when bony ingrowth has been accomplished but it could also be left in indefinitely.

In these designs titantium (unalloyed fibers and alloyed for the load-bearing components) has been used. Titanium has the advantage that alloys and unalloyed metals are generally compatible in a corrosive environment. There are alloys of titanium, one of which is in present use, which are capable of 200,000 psi yield strength. This is more than twice the strength of more conventional prosthetic alloys. On the other hand, unalloyed titanium is soft, and extremely deformable, as is needed in the molding of precision-dimensioned parts. Titanium in the wire and rod forms needed are readily available commercially.

Design of Human Protheses

Since the anatomy of the femur, tibia and humerus of the baboon is similar but miniaturized in comparison with the human, the problem of design is essentially one of a scale-up. We have already constructed dies for molding larger sleeves of porous sintered titanium and demonstrated that the process of manufacture is essentially the same. We have, in fact, made several sizes of full scale prostheses of the tubular design complete with titanium medullary rod, plates and screws. We are capable of making all the parts (except screws which are available on the market) in our laboratories for reconstruction of segments (including knee fusion) up to 7 inches in length. This is not a defined limit but only the largest we have made. The plates have been designed to serve different segment lengths and to be applied using the AO compression device. The human prosthesis designs which we have made are very strong and should last the life of the patient without mechanical failure.

Personnel and Responsibility

We are proposing a clinical trial and study of the use of a fiber-metal implant as a scaffold to allow induction of iliac autogenous bone grafts to restore the osseous integrity of the area of segmental resection and allow for reconstruction of the limb following radical en bloc resection of primary tumors of the long bones. Although the basic design concept for fiber-metal implants segmental replacement are available, the actual fabrication of the hardware depends largely on individual cases. Careful analysis is essential for optimal results. The personnel responsible for proposed studies are listed below:

Principal Investigator: Jorge Galante, M.D.

Co-Investigators: Ken Kuo, M.D., William Rostoker, Ph.D.
Thomas Andriacchi, Ph.D.

Appendix I will include the data collection form. Appendix 2 is the informed consent form. Each patient will be asked to sign this after an explanation of the experimental nature, the risks and the anticipated post-operative course of the segmental replacement.

Patient Selection

1. Age. All patients must be at or near skeletal maturity as determine by standard radiographic criteria. A patient will be rejected if it is determined that growth arrest at that time would result in functional handicap defined as 1 1/2" or greater limb length discrepancy. This provision may be altered or excluded at a later date, but is included here so as to avoid condemnation of the prosthesis on the basis of functional inadequacy.
2. Sex. Males and females will be included in the study.
3. Health. Patients must be free of any physical condition that might impair healing, promote infection or limit life expectancy other than the disease for which the procedure is being undertaken.
4. Pathology. This procedure will be offered only to those patients who according to the principles of oncologic surgery would be considered to have locally resectable lesions. This would include a resectable, locally invasive, malignant tumor, as a low-grade chondrosarcoma, fibrosarcoma, parosteal osteogenic sarcoma, certain recurrent aggressive benign lesions compromising the integrity of the joint with soft tissue extension may be considered such as an extensive giant cell tumor. It

will not be offered to patients in whom an alternative form of therapy (other than amputation) has a reasonable chance of success, or to those patients in whom amputation is the obvious treatment of choice.

5. Because this procedure is applied to the treatment of malignant and extensive agressive benign lesions, the alternatives are few. They include:

   a. Primary amputation of the extremity. This is the usual treatment at the present time, and will be the alternative of choice should segmental replacement fail.

   b. Local resection and replacement with cadaver bone. Because of inherent problems with rejection and mechanical failure, we have no enthusiasm for this method of treatment.

   c. Local resection with or without autogenous bone graft. If this alternative offers a reasonable chance for cure, it will be performed. Segmental replacement is designed for lesions that are too extensive for less radical therapy; therefore, local resection is not a real alternative, and is listed here to make just that point.

   d. Radiation therapy. In cases where radiation therapy has reasonable likelihood of being curative, it will be elected instead of fiber-metal replacement.

Potential Benefits

Reconstruction of the bone and restoration of function and appearance to the extremity as well as cure of the underlying pathology are the chief benefits expected. This procedure offers an alternative to amputation above the affected level.

Initial Work Up

1. Through history and physical examination including adequate functional analysis of all extremities with special attention to the one in question.
2. Routine studies
    a. SMA-18
    b. Urinalysis
    c. Coagulation profile
    d. CBC
    e. EKG
    f. Chest X-ray
    g. PPD skin test
    h. FTA-ABS
    i. Erythrocyte sedimentation rate
3. Special studies
    a. Hand films for bone age (in patients less than 20 years old)
    b. Biopsy of lesion unless already performed
    c. Adequate x-ray studies of lesion as well as films of affected bone for precise measurement
    d. Metastatic work up
        1. bone scan
        2. bone survey if indicated by bone scan
    e. Frozen and permanent sections of tumor at time of surgery
    f. Prophylactic antibiotics - Keflin 1 gram IV q 6 hours 24 hours before surgery to 4 days post-op

Pre-operative Evaluation

1. Thorough history and physical examination including adequate functional analysis of all extremities with special attention to the one in question.
2. Routine studies
3. Special studies
   a. Hand films for bone age (patients less than 20 years old)
   b. Biopsy of lesion unless already performed
   c. Adequate x-ray studies of lesion as well as films of affected bone for precise measurement
   d. Metastatic work up
      1. bone scan
      2. bone survey if indicated by bone scan
   e. Frozen and permanent sections of tumor at time of surgery

Operative Management

The pre-operative preparation of the patient and the operating room environment will follow the standarized procedure utilized for total joint replacement and methacrylate surgery at this institution. The surgery will follow the well-established principles of oncological surgery. The initial stage of the procedure is a radical en bloc segmental resection. Each case must be individualized and the approach must be carefully planned.

In addition to normal cancer surgery principles, certain other principles must be adhered to in insertion of fiber-metal prosthetic segments. They include:

1. Preparation of bone ends to insure intimate contact between bone and fiber metal.
2. Good compression of fragments to add stability and to deform the ends of the fiber-metal segment for optimum contact.
3. Adequate bone graft.
4. The fiber-metal implant will be made to correspond to the segment of bone removed. The fiber-metal segment is placed in the segmental defect and a standard intramedullary rod is inserted across the defect in the usual technique. A compression plate is placed along the lateral surface of the bone and attached proximally with two screws that pass on either side of the intramedullary rod and cross both cortices after tapping appropriate holes. A standard Mueller compression apparatus is attached distally and tightened until the system is stable and the proximal and distal ends of the fiber-metal segment have deformed to give intimate contact with the bone ends. The distal end of the plate is attached and the compression apparatus removed. Necessary modifications of the technique will be made depending on whether the site of segmental resection involves the tibia, the humerus or the femur. Methylmethacrylate will be used for additional fixation if required. Following insertion and fixation of the fiber-metal segment, the wound is copiously irrigated with neomycin solution. Match sticks of cortical cancellous autogenous iliac grafts are placed along the entire segment of fiber metal and 360^{0} around the circumference and are held in place with chromic sutures. The wound is closed in layers taking care to cover the subcutaneous portions of the segment with muscle. Prophylactic antibiotics will be given according to the total joint replacement protocol.

Postoperative Management

1. Routine postoperative care including immediate post-op x-rays of operated extremity, CBC.
2. Immobilization. This will be tailored to the individual case. It is anticipated that this will mean hip spica cast for femoral replacements, long-leg cast for tibial segments and sling for humeral segments. It is further anticipated that patients with tibial segment replacement will be able to be managed with a PTB (patellar tendon bearing) type of cast after six to eight weeks of long-leg cast immobilization.
3. Ambulation and physical therapy. Regimens for fractures of the corresponding bones will be followed for segmental replacement, but the time periods will probably be extended somewhat to allow for bone ingrowth.
4. Discharge and laboratory studies
   a. CBC
   b. SMA-18
   c. ESR

Follow-up Evaluation

1. Frequency of office visits. Patients will be seen at two weeks and four weeks post-discharge, and thereafter at monthly intervals.
2. Frequency of radiographic examinations. X-rays will be taken on the days of the first three office visits, and then at the discretion of the attending surgeon.
3. Radiologic evaluation. A-P and lateral x-rays are taken immediately postoperatively, monthly for three months and then at the discretion of the attending surgeon. Each set of films is graded with respect to contact between bone and prostheses, and to callus formation as follows:

a. Contact grading:

1. good contact with one end of rod only
2. good contact with both ends of rod only
3. good contact with both ends of rod and one interface only
4. good contact with both ends of rod and both interfaces

b. Callus grading:

1. no callus
2. minimal callus at one end only
3. minimal callus at both ends
4. callus at both ends with some extension to mid-rod (diaphysis)
5. good callus throughout

Attendant Discomforts and Risks

Discomfort should be the same as for any fracture that is treated with open reduction and internal fixation. As with many standard orthopedic procedures, other risks will be present. They include:

1. Infection. As in standard orthopedic procedures requiring implantation of foreign bodies, there is a possibility (less than 1%) of deep wound infection that would necessitate removal of the prosthetic segment. In the case of skeletal segmental endoprostheses this would probably necessitate amputation, which is the only reasonable alternative in the first place. If this occurs after the bone has healed, it is possible that the level of amputation would have to be 1-2 inches higher than if primary amputation had been done. To minimize the risk of infection, patients will be given prophylactic antibiotics pre- and post-operatively, and all surgery will be done in the laminar air flow room.

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER
HUMAN INVESTIGATION COMMITTEE

Notice of Approval for Investigation Involving Human Beings

PRINCIPAL INVESTIGATOR: Jorge Galante, M.D. DEPARTMENT: Orthopedic Surgery

TITLE OF PROJECT: Skeletal Segmental Replacement with Sintered Fiber Metal Endoprosthesis
(and Number, if applicable)

TITLE OF PROTOCOL: Fiber Metal Protocol
(and Number, if applicable) Human Application of Fiber Metal

TYPE OF PROJECT: [ ] Grant [ ] Contract [ ] Fellowship [ ] Training Grant
[ ] Other: Specify, Departmental

The above application for approval of clinical investigation involving human beings has been reviewed by the Human Investigation Committee. It is approved as appropriate and ethical with regard to:
(1) The guaranteed protection of the rights & welfare of the human beings involved;
(2) An appropriate method for obtaining informed consent of the participants;
(3) Potential risks and medical benefits; and,
(4) [x] Humans at risk [ ] Humans not at risk.

In the details of separate protocols, the investigator has the individual responsibility to secure the above rights and consent, to use procedures that allow minimum risk, and by his conduct to adhere to and sustain:
(1) "The Recommendations Guiding Physicians in Clinical Research," known as THE DECLARATION OF HELSINKI, adopted by the World Health Organization within the Proceedings of the XVIII World Medical Association;
(2) "The Recommendations for Investigation on Normal Volunteers," in accordance with the guidelines adopted by the Human Investigation Committee, Rush-Presbyterian-St. Luke's Medical Center, February 1, 1972;" and.
(3) "The Protection of Human Subjects," Rules and Regulations as published in THE FEDERAL REGISTER, Volume 40, No. 50, Thursday, March 13, 1975.

APPROVAL IS GRANTED FOR ONE YEAR. Projects extending beyond one year must resubmit annually for the approval of the Human Investigation Committee. Any anticipated changes in protocol during the course of the project must receive prior approval of the Human Investigation Committee.

Member Rev. Bernard A. Pennington
Member Floyd A. Davis, M.D.
Member Rev. Christian A. Hoyde
Member OUT OF TOWN Sue Hegyvary, Ph.D.
Member Harold A. Paul, M.D.
Member Attorney L. Edward Bryant
Member Max E. Rafelson, Ph.D.
Member Shannon Thompson
Member Mortimer Niemark, D.D.S.
Member
Member Janet Wolter, M.D.
Chairman Paul E. Carson, M.D.

DATE: 12-18-75

F-004-70
REV 4/75

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER
HUMAN INVESTIGATION COMMITTEE

Application for Committee Review and Approval

Clinical Research and Investigation Involving Human Subjects

All investigators in studies involving human beings as investigative subjects, regardless of the source of funding, must provide the following information for review and approval by the Human Investigation Committee. Please submit an original and six copies of this completed application, signed by the Principal Investigator and the Department Chairman (if more than one department is involved, signatures of all Chairmen are required) to the Office of Research Affairs with any applicable grant applications, research protocol and budget.

The Committee is charged by federal and state law with this review on behalf of the Medical Center, and may request any additional information it deems necessary before acting on an application.

DO NOT ANSWER THE QUESTIONS BELOW BY REFERRING TO ATTACHMENTS ALONE.
Please type

PRINCIPAL INVESTIGATOR(S): Jorge Galante, M.D. and William Rostoker, Ph.D.

DEPARTMENT (*and* SECTION *if applicable*): Orthopedic Surgery (Galante); Materials Engineering, University of Illinois (Rostoker)

TITLE OF PROJECT: Skeletal Segmental Replacement With Sintered Fiber Metal Endoprosthesis
(*and # if applicable*)

TITLE OF PROTOCOL: Fiber Metal Protocol and Human Application of Fiber Metal
(*and # if more than one*)

SOURCE OF FUNDS: Departmental .
(*if NIH, specify Institute*)

TYPE OF APPLICATION:
[ ] Grant
[ ] Contract
[ ] Fellowship
[x] Departmental
[ ] Research Career Development
[X] Human Investigation Committee Only
[ ] Training Grant
[ ] Other _____

PROJECT PERIOD: Starting Date: October 27, 1975
Ending Date: Continuing

GRANT PERIOD Starting Date: October 27, 1975
Ending Date: Continuing

1. Is an abstract of the project provided in an attached protocol? [x] Yes [ ] No
If not, please provide a one paragraph description of the project in the space provided below:

2. (a) What kinds of patients or subjects are involved in this study? (b) How will they be selected? (c) How will they be involved?

Patients at or near skeletal maturity with a locally invasive malignant tumor (e.g. giant cell tumor, fibrosarcoma) that is presently treated by amputation and in whom limb reconstruction is not possible by standard methods. See attached protocol.

3. (a) Do you plan to use persons other than the principal or co-investigator to obtain informed consent? [ ] Yes [x] No If yes, list individual(s): [The investigator is obligated to furnish instructions and consent form in the native language of the individual concerned in the case of those individuals who do not speak English. An interpreter, competent in the individual's native language, must be available during the explanation of the project. *Please refer to the current suggested consent form, and attach a copy of the actual form to be used in this project. See Federal Register, March 13, 1975, Section 46.3 (c) for definition of informed consent.*]

Name	*Title or position*
Name	*Title or position*

(b) How do you plan to obtain informed consent?

Committee guidelines have been followed in drawing up a consent form that the patient or legal guardian will sign (see attached). The patient will be given adequate time and opportunity to read the consent, consider alternatives and ask questions of the attending surgeon.

(c) How is the consent to be documented?

See enclosed consent form.

4. Outline the potential diagnostic and/or therapeutic benefit to the patient if the study is clinical research combined with professional care.

Potential therapeutic benefit includes reconstruction of an extremity to normal or near-normal function and appearance in cases where amputation or no therapy at all are the only alternatives.

5. Outline the scientific benefit of the study.

In vivo human evaluation of a prosthetic bone segment that has been proven effective in baboons and other animals.

6. Outline any potential hazards to patients, including knowledge of toxicities of any agents to be used; and where known, outline the prevalence of injurious effects and the severity of the hazard.

1. Infection. As in standard orthopedic procedures requiring implantation of foreign bodies, there is a possibility (less than 1%) of deep wound infection that would require removal of the prosthetic segment. In the case of skeletal segmental endoprostheses this would probably necessitate amputation, which is the only reasonable alternative in the first place. If this occurs after segmental replacement, it is possible that the level of amputation would have to be 2-4 cm. more proximal than if primary amputation had been done. To minimize the risk from infection, patients will be given prophylactive antibiotics pre and post-operatively, and all surgery will be performed in a laminar air flow room.
2. Standard operative risks, e.g. blood loss, anesthetic, etc.
3. Failure of prosthesis. As in many orthopedic procedures, the possibility of non-union and fracture of the prosthesis itself are possible complications. There is no reason to believe that there is more than the ordinary chance of either of these occurring with this particular prosthesis.
4. Teratogenesis. This is a remote possibility, and is a function of the alloy that comprises the prosthesis and not the prosthesis itself. Titanium is used extensively in the U.S. and in Europe without apparent problem. Women of child-bearing age will be apprised of these facts, but will not be excluded from this study.
5. Carcinogenesis. Possible carcinogenic effects of titanium are being investigated in this laboratory at the present time. It is not possible for anyone to state what the risks are in this regard. The same can be said of the materials that comprise standard total joint replacements in wide use

6. (cont.)

today. As in other cases, the risks must be weighed against the potential benefits, and the patient will be apprised of them and make the final decision.

7. (*This question relates only to protocols involving investigational drugs.*) Give below the new drug number(s) issued by the U.S. Food and Drug Administration, and describe the current FDA status of each drug or substance to be used. [Please be aware of the Federal requirement to report any adverse reactions to DHEW immediately.]

Investigational New Drug:* [ ] Yes [xx] No

If yes, complete the State of Illinois Investigational New Drug Form, and complete information below.

Name of Drug: _____ IND Number _____

FDA Status: [ ] Phase I [ ] Phase II [ ] Phase III

IND Forms Filed: [ ] FDA 1571 [ ] FDA 1572 [ ] FDA 1573

Date of 30-day Expiration or FDA Waiver: _____

FDA Restriction: _____

**If more than one drug is being used, repeat the above format on a separate page, and append to this form. Information should by typed or printed.*

8. If the study will include any of the following subjects, please check. If the study will not include any such subjects, check "None of these groups."

[x] minors (Under age 18) [ ] prisoners [x] pregnant women

[ ] incompetents or the mentally infirm [ ] the unborn

[ ] None of these groups

Add here any special protective measures which are being taken to protect the rights of subjects noted above:

Full informed consent of the patient, or of the parent or guardian in cases of minors will be obtained in all cases. As stated, it is not anticipated that the skeletally immature will be considered in this particular study.

9. (a) Is a biopsy involved? [x] Yes [ ] No

If yes, of what? X

For what purpose is the above procedure being performed?
[x] diagnostic [ ] therapeutic [ ] research

(b) Is a blood sample involved? [ ] Yes [x] No

If yes, how much? _____ how often? _____

For what purpose is the above procedure being performed?
[ ] diagnostic [ ] therapeutic [ ] research

(c) Are body fluids involved? [ ] Yes [xx] No

If yes, of what? _____

how much? _____ how often? _____

For what purpose is the above procedure being performed?
[ ] diagnostic [ ] therapeutic [ ] research

SIGNATURES:
(*Type name below signature line.*)

Principal Investigator

Department Chairman

William Hepra
Institutional Official

Date

F-002/70
REV 4/75

RUSH-PRESBYTERIAN-ST. LUKE'S MEDICAL CENTER
HUMAN INVESTIGATION COMMITTEE

I, _____, an adult (or: legal guardian of _____, a minor), have been invited to participate in a study of skeletal segmental replacement with sintered fiber metal endoprosthesis under the direction of Jorge Galante, M.D. in which I voluntarily consent to participate.

a. The implications of my voluntary participation in this medical investigation, its nature, duration and purpose, the methods and means by which it is to be conducted, and the inconvenience and hazards which may be expected have been thoroughly explained to me by _____ _____.

b. I have read and understand all written materials which have been provided to me further describing the study and its potential risks and benefits to me.

c. I have been given an opportunity to ask any questions I wish concerning this procedure and all such questions have been answered to my complete satisfaction. I understand that my participation in this study can be terminated at any time upon my request.

d. (If not applicable check ☐.) I certify that, to the best of my knowledge, I am not pregnant at this time. I agree that if I become pregnant during the course of this study I will notify _____, who is directing this study.

_____
Volunteer's signature and date

_____
Relationship

I was present during the explanation referred to above, as well as the Volunteer's opportunity for questions, and hereby witness his consent to participate in the study.

_____
Witness's signature and date

PROTOCOL
Human Application of Fiber Metal

I. Patient Selection

A. Age. All patients must be at or near skeletal maturity as determined by standard radiographic criteria. A patient will be rejected if it is determined that growth arrest at that time would result in functional handicap defined as 1½" or greater limb length discrepancy. This provision may be altered or excluded at a later date, but is included here so as to avoid condemnation of the prosthesis on the basis of functional inadequacy.

B. Sex. Males and females will be included in the study. It is not without some reservation that females of childbearing age are incuded, but there is no known reason why they should be any less acceptable candidates for this procedure than for total joint replacement.

C. Health. Patients must be free of any physical condition that might impair healing, promote infection of limit life expectancy other than the disease for which the procedure is being undertaken.

D. Pathology. This procedure will be offered only to those patients who have a resectable, locally invasive, malignant tumor, i.e. fibrosarcoma, recurrent giant cell tumor, liposarcoma. It will not be offered to patients in whom an alternative form of therapy (other than amputation) has a reasonable chance of sucess or to those patients in whom amputation is the obvious treatment of choice

II. Initial Workup

A. Thorough history and physical examination including adequate functional analysis of all extremities with special attention to the one in question.

B. Routine Studies.

1. SMA-18
2. Urinalysis
3. Coagulation profile
4. CBC
5. EKG
6. Chest x-ray
7. PPD skin test
8. FTA-ABS
9. Erythrocyte sedimentation rate

C. Special studies

1. Hand films for bone age (in patients less than 20 years old)
2. Biopsy of lesion unless already performed.
3. Adequate x-ray studies of lesion as well as films of affected bone for precise measurement.
4. Metastatic workup
   a. Bone scan
   b. Bone survey if indicated by bone scan
5. Frozen and permanent sections of tumor at time of surgery.

6. Prophylactic antibiotics - Keflin 1 gram IV q 6 hours 24 hours before surgery to 4 days post-op

III. Post-Operative Management

A. Routine post-operative care including immediate post-op x-rays of operated extremity, CBC, etc.

B. Immobilization. This will be tailored to the individual case. It is anticipated that this will mean hip spica cast for femoral replacements, long-leg cast for tibial segments and sling for humeral segments. It is further anticipated that patients with tibial segment replacement will be able to be managed with a PTB (patellar tendon bearing) type of cast after 6-8 weeks of long leg cast immobilization.

C. Ambulation and physical therapy. Regimens for fractures of the corresponding bones will be followed for segmental replacement, but the time periods will probably be extended somewhat to allow for bone ingrowth.

D. Discharge laboratory studies

1. CBC
2. SMA-18
3. ESR

IV. Follow-Up Evaluation

A. Frequency of office visits: Patients will be seen at two weeks and four weeks post-discharge, and thereafter at monthly intervals.

B. Frequency of radiographic examination: X-rays will be taken on the days of the first three office visits, and then at the discretion

of the attending surgeon.

C. Functional evaluation and standard screening tests for infection will be performed regularly until there is no further need for them.

PATIENT INFORMATION SHEET

Skeletal Segmental Replacement with Sintered Fiber Metal Endoprosthesis

1. Explanation of Procedure

The procedure consists of:

a. Removal of an appropriate segment of affected bone, leaving intact the muscles, vessels, nerves and tendons that surround the bone unless they too are affected by the underlying tumor, in which case they must also be removed;

b. Replacement of the segment of bone with a specially designed prosthetic segment. This segment is made of standard orthopedic materials, but the design is new. The segment has been tested in laboratory animals with good results, but has not yet been proven in humans;

c. Fixation of the segment with a compression apparatus and inclusion of autogenous iliac bone graft;

d. Appropriate post-operative immobilization;

e. The segment is designed to become incorporated into bone, and therefore removal is not anticipated. It should be assumed that the segment will be left in place.

2. Attendant Discomforts and Risks

Discomfort should be the same as for any fracture that is treated with open reduction and internal fixation. As with many standard orthopedic procedures, other risks will be present. They include:

a. Infection. As in standard orthopedic procedures requiring

implantation of foreign bodies, there is a possibility (less than 1%) of deep wound infection that would necessitate removal of the prosthetic segment. In the case of skeletal segmental endoprostheses this would probably necessitate amputation, which is the only reasonable alternative in the first place. If this occurs after the bone has healed, it is possible that the level of amputation would have to be 1-2 inches higher than if primary amputation had been done. To minimize the risk of infection, patients will be given prophylactic antibiotics pre- and post-operatively, and all surgery will be done in the laminar air flow room.

b. Standard operative risks. All surgery carries with it the possibility of blood loss, anesthetic problems, etc. These things will be explained on an individual basis, but are no different for this procedure than for other operations on major bones.

c. Failure of prosthesis. As in many orthopedic procedures, the possibility of non-union (or the failure of the bone to knit properly) and fracture of the prosthesis itself are possible complications. There is no reason to believe that there is more than the ordinary chance of either of these occurring with this particular prosthesis.

d. A very remote possibility exists that a foreign implant present in the body for forty or more years could become cancerous. No one has every shown that this is possible, and it has never occurred with the metals used in orthopedic surgery up-to-date.

e. A very remote possibility exists that congenital malformations could occur in children from a patient that has an internal prosthesis. It has never occurred to date with any of the implants used in orthopedic surgery.

3. Potential Benefits

Reconstruction of the bone and restoration of function and appearance to the extremity as well as cure of the underlying pathology are the chief benefits expected. This procedure offers an alternative to amputation above the affected level.

4. Alternatives

Because this procedure is applied to the treatment of malignant tumors, the alternatives are few. They include:

a. Primary amputation of the extremity. This is the usual treatment at the present time, and will be the alternative of choice should segmental replacement fail.

b. Local resection and replacement with cadaver bone. Because of inherent problems with rejection and mechanical failure, this method of treatment has been abandoned in this institution.

c. Local resection with or without autogenous bone graft. If this alternative offers a reasonable chance for cure, it will be performed. Segmental replacement is designed for lesions that are too extensive for less radical therapy; therefore, local resection is not a real alternative, and is listed here to make just that point.

d. Radiation therapy. In cases where radiation therapy has a reasonable likelihood of being curative, it will be elected instead of fiber metal replacement.

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